

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re: U.S. Patent No. 7,138,501  
Inventor(s): Ruben et al.  
Issued: November 21, 2006  
Applicant: Human Genome Sciences Inc.  
Docket No.: PF523P1  
FDA Approval: BLA 125370 (BENLYSTA® (belimumab))

Mail Stop Hatch-Waxman PTE  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156**

Dear Sir:

Pursuant to 35 U.S.C. § 156, Human Genome Sciences Inc. (hereinafter "HGS") hereby requests an extension of the term of U.S. Patent No. 7,138,501 (the '501 Patent). HGS is the assignee of the entire right, title and interest in the above-captioned patent by virtue of an assignment to HGS recorded on March 8, 2002 at reel 012660, frame 0444, and a chain of title recorded on March 13, 2003 at reel 013847, frame 0919 and at reel 013847, frame 0928. By the Power of Attorney enclosed herein (Attachment A), Applicant appoints the Practitioners at Customer Number 24633, including Kevin Shaw, as attorneys for HGS with regard to this application for extension of term of the '501 Patent and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

HGS hereby provides the following information as required by 37 C.F.R. § 1.740.

**1. Identification of the Approved Product [§ 1.740(a)(1)]:**

The approved product BENLYSTA® (belimumab) is a recombinant fully human IgG<sub>1</sub>λ monoclonal antibody that specifically binds to soluble human B Lymphocyte

Stimulator (BLyS). Belimumab is produced by NS0 mouse myeloma cells in serum-free cell culture production medium and has an approximate molecular weight of 147 kDa. BENLYSTA is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for intravenous infusion.

**2. Federal Statute Governing Regulatory Approval of the Approved Product [§ 1.740(a)(2)]:**

The approved product was subject to regulatory review under, *inter alia*, the Public Health Service Act (42 U.S.C. § 201 *et seq.*) and the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355 *et seq.*).

**3. Date of Approval for Commercial Marketing [§ 1.740(a)(3)]:**

The approved product BENLYSTA received approval for commercial marketing or use under § 351 of the Public Health Service Act on March 9, 2011. A copy of the FDA approval letter (as released by the FDA with confidential commercial information redacted) is attached (Attachment B).

**4. Identification of Active Ingredient and Certifications Related to Commercial Marketing of Approved Product [§ 1.740(a)(4)]:**

The active ingredient of BENLYSTA is belimumab, which has not been approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to the approval granted on March 9, 2011 to the present Applicant. A copy of the package insert describing the approved product is attached (Attachment C).

**5. Statement Regarding Timeliness of Submission of Patent Term Extension Request [§ 1.740(a)(5)]:**

This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted sixty (60) day period pursuant to 37 C.F.R. § 1.720(f). The last day on which this application may be submitted is May 7, 2011.

**6. Complete Identification of the Patent for Which Extension is Being Sought [§ 1.740(a)(6)]:**

Listed Inventors: Steven M. Ruben, Gil H. Choi, Tristan Vaughan, David Hilbert

Patent No.: 7,138,501

Issue Date: November 21, 2006

Expiration Date: July 9, 2023<sup>1</sup> (without extension under 35 U.S.C. §156)

**7. Copy of the Patent for Which an Extension is Being Sought [§ 1.740(a)(7)]:**

A copy of the '501 Patent is attached (Attachment D).

**8. Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payment, or Reexamination Certificate [§ 1.740(a)(8)]:**

No disclaimer or reexamination certificate has been issued on this patent. A copy of the certificate of correction issued on March 6, 2007 is provided as Attachment E. A copy of the Maintenance Fee Statement indicating the timely payment of relevant maintenance fees to date is provided as Attachment F.

**9. Statement Regarding Patent Claims Relative to Approved Product [§ 1.740(a)(9)]:**

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<sup>1</sup> Includes patent term adjustment under 35 U.S.C. 154(b) of 754 days as listed on the face of the '501 Patent. A Petition for Reconsideration of Patent Term Adjustment is pending before the United States Patent and Trademark Office, and a Complaint filed in the United States District Court for the District of Columbia is also pending, in each case seeking correction of the patent term adjustment for the '501 Patent from 754 days to 1,135 days. Including the requested patent term adjustment correction, the '501 Patent would expire July 24, 2024.

*The statements below are made solely to comply with the requirements of 37 C.F.R. § 1.740(a)(9). Applicant notes that, as the M.P.E.P. acknowledges, § 1.740(a)(9) does not require an applicant to show whether or how the listed claims would be infringed, and that this question cannot be answered without specific knowledge concerning acts performed by third parties. As such, these comments are not an assertion or an admission of Applicant as to the scope of the listed claims, or whether or how any of the listed claims would be infringed, literally or under the doctrine of equivalents, by the manufacture, use, sale, offer for sale or the importation of any product.*

At least claims 1-2, 4-10, 14-24, and 29-36 of the '501 Patent claim the approved product, namely, the active pharmaceutical ingredient in BENLYSTA.

Claim 1 reads as follows:

An isolated antibody that immunospecifically binds B Lymphocyte Stimulator protein wherein said antibody comprises a first amino acid sequence at least 85% identical to amino acid residues 1-123 of SEQ ID NO:327 and a second amino acid sequence at least 85% identical to amino acid residues 141-249 of SEQ ID NO:327 and wherein said B Lymphocyte Stimulator protein is selected from the group consisting of:

- (a) a protein whose amino acid sequence consists of amino acid residues 1-285 of SEQ ID NO:3228;
- (b) a protein whose amino acid sequence consists of amino acid residues 134-285 of SEQ ID NO:3228; and
- (c) a trimer of the protein of (b).

Claim 1 of the '501 Patent reads on the active ingredient in BENLYSTA as the active ingredient (belimumab) meets all the limitations of the claim. The active ingredient (belimumab) is a recombinant fully human IgG<sub>1</sub>λ monoclonal antibody that specifically binds to soluble human B Lymphocyte Stimulator (BLyS). See Attachment C. Soluble human BLyS is a protein, predominantly found as a trimer, whose amino acid sequence consists of amino acid residues 134-285 of SEQ ID NO:3228. The amino acid sequence of belimumab comprises amino acid residues 1-123 of SEQ ID NO: 327 of the '501 Patent and amino acid residues 141-249 of SEQ



ID NO: 327 of the '501 Patent. *See* Sequence listing of the '501 Patent (Attachment D).

Accordingly, belimumab meets all of the limitations of claim 1 of the '501 Patent.

10. **Relevant Dates Under 35 U.S.C. § 156 for Determination of Applicable Regulatory Review Period [37 C.F.R. § 1.740(a)(10)]:**

The relevant dates and information pursuant to 35 U.S.C. § 156(g) are as follows:

Investigational New Drug Application (BB-IND No. 9970) for BENLYSTA was filed on August 15, 2001 and became effective on October 23, 2001. A copy of the letter from the FDA reflecting the effective date of this IND is provided as Attachment G.

Original Biologics Licensing Application for BENLYSTA (BLA 125370) was submitted on June 10, 2010.

Biologics License No. 1820 for BENLYSTA was issued on March 9, 2011. A copy of the approval letter (as released by the FDA with confidential commercial information redacted) is provided as Attachment B.

**11. Summary of Significant Events During Regulatory Review Period [§ 1.740(a)(11)]:**

A summary of the significant activities undertaken by Applicant during the regulatory review period with respect to the approved product is provided below. Further, a description of various clinical trials conducted by Applicant during the regulatory review is annexed hereto as Attachment H. Applicant reserves the right to supplement the chronology with materials from which it was derived or other evidence related to Applicant's conduct in obtaining the approval of BENLYSTA as provided by 21 C.F.R. § 60.32.

On August 15, 2001, HGS submitted to the FDA an investigational new drug application for a recombinant human monoclonal antibody (belimumab) that specifically binds human B Lymphocyte Stimulator Protein. The antibody was developed as a potential new therapeutic for the treatment of autoimmune disease.

On September 13, 2001, FDA placed BB-IND 9970 on clinical hold.

On October 23, 2001, FDA communicated to HGS via telephone that the clinical hold was removed, thus making BB-IND 9970 effective, as confirmed by a communication mailed to HGS on October 30, 2001 (Attachment G).

From approximately October 23, 2001 until approximately April 20, 2010, a series of Phase I, II, and III clinical trials were conducted.

On January 20, 2003, HGS submitted to the FDA a request for Fast Track Designation.

On March 6, 2003, representatives from HGS and CBER participated in an end-of-Phase I meeting.

On March 13, 2006, representatives from HGS and CBER participated in an end-of-Phase II meeting.

On January 22, 2010, representatives from HGS and CBER participated in a Pre-BLA meeting.

On June 10, 2010, HGS submitted a biologics licensing application for BENLYSTA (BLA 125370).

On March 9, 2011, FDA approved BLA 125370, issuing marketing authorization for BENLYSTA (Attachment B).

**12. Statement Concerning Eligibility for and Duration of Extension Sought Under 35 U.S.C. § 156 [37 C.F.R. § 1.740(a)(1)]:**

Applicant is of the opinion that U.S. Patent No. 7,138,501 is eligible for extension based upon meeting the requirements under 35 U.S.C. § 156 as follows:

- (a) 35 U.S.C. § 156(a): U.S. Patent No. 7,138,501 claims a product.
- (b) 35 U.S.C. § 156(a)(1): U.S. Patent No. 7,138,501 has not expired before the submission of this application.
- (c) 35 U.S.C. § 156(a)(2): The term of U.S. Patent No. 7,138,501 has never been extended under 35 U.S.C. § 156(e)(1).
- (d) 35 U.S.C. § 156(a)(3): The application for patent term extension is submitted by the owner of record of the patent in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d) and the rules of the Patent and Trademark Office.
- (e) 35 U.S.C. § 156(a)(4): The product BENLYSTA has been subject to a regulatory review period before its commercial marketing or use.
- (f) 35 U.S.C. § 156(a)(5)(A): The commercial marketing or use of the product BENLYSTA after the regulatory review period is the first permitted commercial marketing or use under the provisions of § 351(a) of the Public Service Act.
- (g) 35 U.S.C. § 156(c)(4): No other patent has been extended for the same regulatory review period for the product BENLYSTA.

- (h) 35 U.S.C. § 156(d)(1): This application is submitted within the permitted 60 day period beginning on the date the product first received permission for commercial marketing or use.

Applicant respectfully submits that the term of U.S. Patent No. 7,138,501 should be extended from July 9, 2023<sup>2</sup> up to and including March 9, 2025, or 610 days. This extension was calculated per 37 C.F.R. § 1.775 as follows:

- (a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on October 23, 2001 and ended on March 9, 2011, which is a total of 3426 days, which is the sum of (1) and (2) below:
- (1) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the “Testing Period,” began on October 23, 2001 and ended on June 10, 2010, which is 3153 days; and
- (2) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii), the “Approval Period,” began on June 10, 2010 and ended on March 9, 2011, which is 273 days.
- (b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in (a) less 2504 days, which is the sum of (1) – (3) below:
- (1) The number of days in the regulatory review period which were on or before the date on which the patent issued (November 21, 2006), which is 1856 days; and
- (2) The number of days during which Applicant did not act with due diligence, which is zero days; and

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<sup>2</sup> As noted *supra*, Applicant is seeking corrected patent term adjustment for the ‘501 Patent from 754 days to 1,135 days; the corrected expiration date would be July 24, 2024.

- (3) One half the number of days determined in subparagraph (a)(1) above after the patent issued, which is 648 days;
- (c) The number of days as determined in (a) minus (b) above (922 days) when added to the original term of the patent (July 9, 2023<sup>3</sup>) would result in the date of January 16, 2026.
- (d) Fourteen years when added to the date of issuance of the Biologics License (March 9, 2011) would result in the date of March 9, 2025.
- (e) The earlier date as determined in (c) and (d) above is March 9, 2025.
- (f) Since U.S. Patent No. 7,138,501 issued after September 24, 1984, the period of extension may not exceed five years from the original expiration date of July 9, 2023. Five years added to July 9, 2023 would result in a date of July 9, 2028.
- (g) The earlier date as determined in (e) and (f) above is March 9, 2025.
- 13. Statement Pursuant to 37 C.F.R. § 1.740(a)(13):**
- Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.
- 14. Applicable Fee [§ 1.740(a)(14)]:**
- The transmittal document filed herewith authorizes the U.S. Patent and Trademark Office to charge the prescribed fee pursuant to 37 C.F.R. §1.20(j) for receiving and

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<sup>3</sup> As noted *supra*, Applicant is seeking corrected patent term adjustment for the '501 Patent from 754 days to 1,135 days; the corrected expiration date would be July 24, 2024.

acting upon the application for extension to the deposit account associated with the undersigned attorney.

**15. Name and Address for Correspondence [§ 1.740(a)(15)]:**

Please address all correspondence to:

Kevin Shaw  
Hogan Lovells US LLP  
Columbia Square  
555 Thirteenth Street, NW  
Washington, District of Columbia 20004  
Phone: 202-637-6466  
Fax: 202-637-5910  
Email: kevin.shaw@hoganlovells.com


The correspondence address for U.S. Patent No. 7,138,501 is unchanged for all other purposes. A Power of Attorney granted to the undersigned, a copy of which is included as Attachment A, accompanies this communication.

Two additional copies of this application are enclosed, in compliance with 37 C.F.R. § 1.740(b).

If this application for extension of patent term is held to be informal, Applicant may seek to have that holding reviewed by filing a petition with the required fee, as necessary, pursuant to 37 C.F.R. §§ 1.181, 1.182, or 1.183, as appropriate, within such time as may be set in any notice that the application has been held to be informal, or if no time is set, within one month of the date on which the application was held informal.

Respectfully submitted,

Date: April 8, 2011

  
Kevin G. Shaw (Reg. No. 43,110)

**HOGAN LOVELLS US LLP**  
555 Thirteenth Street, N.W.  
Washington, D.C. 20004  
Telephone: 202-637-6466  
Facsimile: 202-637-5910  
e-mail: kevin.shaw@hoganlovells.com  
**Customer No. 24633**



**Index of Attachments**

<u>Attachment A:</u>	Power of Attorney
<u>Attachment B:</u>	FDA Approval Letter (as released by FDA in redacted form)
<u>Attachment C:</u>	Package Insert for BENLYSTA
<u>Attachment D:</u>	U.S. Patent No. 7,138,501
<u>Attachment E:</u>	Certificate of Correction
<u>Attachment F:</u>	Maintenance Fee Statement
<u>Attachment G:</u>	FDA Letter Regarding Effective Date of IND
<u>Attachment H:</u>	Summary of Clinical Trials

U.S. Patent No. 7,138,501

Application for Patent Term Extension

# **Attachment A**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

U.S. Patent No. 7,138,501

Patentee: Ruben et al.

Issued: November 21, 2006

Docket No.: PF523P1

**POWER OF ATTORNEY OR AUTHORIZATION OF AGENT**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**Statement Under 37 C.F.R. § 3.73**

Human Genome Sciences, Inc. ("HGS"), organized and existing under the laws of the State of Delaware, having its principal place of business at 14200 Shady Grove Road, Rockville, Maryland 20850, states that it is the assignee of record of the entire right, title and interest for the above-identified application by virtue of assignments directed to U.S. Application No. 09/880,748, filed June 15, 2001, that matured into the above-identified patent, and all continuation and divisional applications thereof, as listed in the chain of title below:

1. From: Steven M. Ruben, Steven C. Barash, Gil H. Choi, Tristan Vaughan, and David Hilbert  
To: Human Genome Sciences, Inc.  
The document was recorded in the U.S. Patent and Trademark Office on March 8, 2002, at Reel 012660, Frame 0444.
2. From: Tristan Vaughan  
To: Cambridge Antibody Technology, Ltd.  
The document was recorded in the U.S. Patent and Trademark Office on March 13, 2003, at Reel 013847, Frame 0919.
3. From: Cambridge Antibody Technology, Ltd.  
To: Human Genome Sciences, Inc.  
The document was recorded in the U.S. Patent and Trademark Office on March 13, 2003, at Reel 013847, Frame 0928.

The undersigned, whose title is supplied below, is empowered to sign this document on behalf of HGS. The undersigned has reviewed all the documents in the chain of title of the above-captioned application, and, to the best of the undersigned's knowledge and belief, HGS has title in the application as described above.

**Power of Attorney or Authorization of Agent**

HGS hereby appoints the Practitioners at **Customer Number 24633** as its attorneys or agents for the purpose of prosecuting an Application for Extension of Patent Term Under 35 U.S.C. §156 in connection with U.S. Patent 7,138,501, and to transact all business in the U.S. Patent and Trademark Office only in connection therewith. The correspondence address for the instant patent is unchanged for all other purposes. Please direct all communications for this Application for Extension of Patent Term to Kevin Shaw.

On behalf of Human Genome Sciences, Inc.:

For: Human Genome Sciences, Inc.

Signature: 

Name: James H. Davis

Title: Executive Vice President and General Counsel

Date: 7 Apr 2011

# **Attachment B**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

Our STN: BL 125370/0

**BLA APPROVAL**  
March 9, 2011

Human Genome Sciences, Inc.  
14200 Shady Grove Road  
Rockville, MD 20850

Attention: Diana J. Daly  
Executive Director, Regulatory Affairs

Dear Ms. Daly:

Please refer to your Biologics License Application (BLA) dated June 9, 2010, received June 9, 2010, submitted under section 351 of the Public Health Service Act for Benlysta (belimumab) for injection.

We acknowledge receipt of your amendments dated July 20, August 10 and 27, September 15, 24, 27, and 30, October 6, 13, 19, 25, 26, and 27, November 3, 8, 10, 23, and 30, and December 1, 9, and 21, 2010, and January 28, February 8, 11, 14, 17, 23, and 25, and March 3 and 4, 2011.

We are issuing Department of Health and Human Services U.S. License No. 1820 to Human Genome Sciences, Rockville, Maryland, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce, or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product belimumab. Belimumab is indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

Under this license, you are approved to manufacture belimumab drug substance at Human Genome Sciences, Inc., in Rockville, Maryland. The final formulated product will be manufactured, filled, labeled, and packaged at Hospira, Inc., in McPherson, Kansas. You may label your product with the proprietary name Benlysta and will market it as 120 mg in a 5-mL vial and 400 mg in a 20-mL vial.

Results of ongoing stability studies should be submitted throughout the dating period, as the data become available, including the results of stability studies from the first three production lots.

The dating period for the 120-mg vial of belimumab shall be 36 months from the date of manufacture when stored at 2° to 8°C. The dating period for the 400-mg vial of belimumab shall be 36 months from the date of manufacture when stored at 2° to 8°C. The dating period for drug

substance shall be 36 months when stored at -40° and/or -80°C. Belimumab drug product stability may be extended by inclusion of additional data for pilot lots and commercial lots in the Benlysta annual report.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You are not currently required to submit samples of future lots of belimumab to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of belimumab, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

We are approving this application for use as recommended in the enclosed agreed-upon labeling text and with the minor editorial revision listed below.

- Replace "US License No. 0000" on the carton and container and the "US License No. XXXX" in the package insert and medication guide with "U.S. License No. 1820".

#### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to, except with the revisions listed, the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled *SPL Standard for Content of Labeling Technical Qs and As* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. For administrative purposes, designate this submission "Product Correspondence – Final SPL for approved BLA STN 125370."

The SPL will be accessible via publicly available labeling repositories.

#### **CARTON AND IMMEDIATE-CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate-container labels, except with the revisions listed above, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes,

designate this submission "**Product Correspondence - Final Printed Carton and Container Labels for approved BLA STN 125370.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

#### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 4 years 11 months because necessary studies are impossible or highly impracticable. This is because too few children have the disease condition to study.

We are deferring submission of your pediatric study for ages 5 to 16 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1. Phase 2, multicenter study to evaluate the safety, efficacy, and pharmacokinetics of belimumab plus background standard therapy in 100 pediatric subjects ages 5 years to 17 years of age with active systemic lupus erythematosus (SLE).

Final Protocol Submission:	August 2011
Study Completion Date:	March 2016
Final Report Submission:	October 2016

Submit final reports to this BLA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s).**"

#### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.



We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks related to immunogenicity and negative pregnancy outcomes related to Benlysta (belimumab).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2. Develop improved immunogenicity assays that are less sensitive to product interference that are capable of detecting human anti-human antibodies (HAHA) in the presence of belimumab at ranges that would be expected to occur in patients receiving both high and low doses.

The timetable you submitted on February 11, 2011, states that you will conduct these studies according to the following schedule:

Final Protocol Submission: March 2012  
Final Report Submission: January 2013

3. Conduct a pregnancy registry to evaluate pregnancy outcomes for women exposed to Benlysta (belimumab) during pregnancy.

The timetable you submitted on February 23, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission: July 2011  
Study Completion Date: October 2018  
Final Report Submission: April 2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks related to the potential for Benlysta (belimumab) to interfere with host responses to vaccinations, and to assess a signal of serious risks of mortality, infection, and malignancy with Benlysta (belimumab).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

4. Conduct a randomized clinical trial to evaluate the effects of Benlysta (belimumab) treatment on host response to therapeutic vaccines. B cell-dependent antigens (e.g., pneumococcal polysaccharide vaccine) and T cell-dependent antigens (e.g., tetanus toxoid) will be evaluated.

The timetable you submitted on February 14, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: December 2011  
Trial Completion Date: March 2014  
Final Report Submission: September 2014

5. Conduct a randomized, placebo-controlled clinical trial with Benlysta (belimumab) in 5000 patients with active, autoantibody-positive systemic lupus erythematosus to evaluate Benlysta's long term safety profile including adverse events of special interest (e.g., mortality, malignancy, serious and opportunistic infections and depression/suicidality).

The timetable you submitted on February 23, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: September 2011  
Trial Completion Date: May 2022  
  
Interim Report Submission: May 2019 (1 year data)  
May 2020 (2 year data)  
  
Final Report Submission: May 2023 (5 year data)

Submit the protocols to your IND 9970, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70, requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS  
UNDER SECTION 506B**

We remind you of your postmarketing commitments:

6. Conduct a randomized, controlled clinical trial in patients with lupus nephritis to evaluate the efficacy and safety of Benlysta (belimumab).

The timetable you submitted on February 23, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 2012
Trial Completion:	January 2017
Final Report Submission:	October 2017

7. Conduct a randomized, controlled clinical trial to evaluate the efficacy and safety of Benlysta (belimumab) in African-American patients with SLE.

The timetable you submitted on November 30, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	November 2011
Trial Completion Date:	July 2017
Final Report Submission:	January 2018

8. Submit a final report for the long-term, open-label, continuation trial LBSL99.

The timetable you submitted on February 23, 2011, states that you will conduct this trial according to the following schedule:

Trial Completion Date:	May 2016
Final Report Submission:	December 2016

9. Submit a final report for the long-term, open-label, continuation trial C1066.

The timetable you submitted on February 23, 2011, states that you will conduct this trial according to the following schedule:

Trial Completion Date:	May 2015
Final Report Submission:	December 2015

10. Submit a final report for the long-term, open-label, continuation trial C1074.

The timetable you submitted on February 23, 2011, states that you will conduct this trial according to the following schedule:

Trial Completion Date:	March 2015
Final Report Submission:	October 2015

Submit clinical protocols to your IND 9970 for this product and all final reports to this BLA. In addition, under 21 CFR 601.70, you should include a status summary of each commitment in your annual progress report of postmarketing studies/trials to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING  
REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

11. Submit data supporting microbial control for the UF/DF membrane lifetime studies in a CBE-0 supplement by June 2012.

The timetable you submitted on December 21, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2010
Study Completion Date:	December 2011
Final Report Submission:	June 2012

12. Qualify the capper and validate the integrity of the belimumab drug product container closure in a helium leak test using 5 mL vials prepared at minimum and maximum sealing forces. Information and summary validation data of the helium leak test and the integrity of the belimumab drug product container closure should be submitted in a Changes Being Effected (CBE-0) supplement. Include the preparation of the positive controls and sensitivity (breach size) of the helium leak test.

The timetable you submitted on December 21, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: March 2011  
Study Completion Date: April 2011  
Final Report Submission: June 2011

13. Provide quantitative data to demonstrate removal of soluble contaminants by the vial washing process. The quantitative qualification data should be submitted in a Changes Being Effected (CBE-0) supplement.

The timetable you submitted on December 21, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: March 2011  
Study Completion Date: April 2011  
Final Report Submission: June 2011

Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. In addition, under 21 CFR 601.70, you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."

#### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

We acknowledge receipt of your submissions dated November 23, 2010, and February 23, 2011, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that at this time, a REMS is not necessary for Benlysta (belimumab) to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

#### **REPORTING REQUIREMENTS**

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding, and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Biological product deviations sent by courier or overnight mail should be addressed to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
10903 New Hampshire Avenue, Bldg. 51, Room 4206  
Silver Spring, MD 20903

#### **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

#### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the

proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and the package insert at the time of initial dissemination or publication accompanied by a Form FDA 2253. For instructions on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

#### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this BLA and to the following address:

MedWatch Program  
Office of Special Health Issues  
Food and Drug Administration  
10903 New Hampshire Ave  
Building 32, Mail Stop 5353  
Silver Spring, MD 20993

#### **POST-ACTION FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Philantha M. Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,

A handwritten signature in black ink, appearing to read 'CJR', with a long horizontal flourish extending to the right.

/Curtis J. Rosebraugh, M.D., M.P.H./

Curtis J. Rosebraugh, M.D., M.P.H.

Director

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Enclosures:

Content of Labeling

Carton and Container Labeling



## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BENLYSTA safely and effectively. See full prescribing information for BENLYSTA.

### BENLYSTA® (belimumab)

for injection, for intravenous use only  
Initial U.S. Approval: 2011

## INDICATIONS AND USAGE

BENLYSTA is a B-lymphocyte stimulator (BLyS)-specific inhibitor indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. (1, 14)

**Limitations of Use:** The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus (1). BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide (1). Use of BENLYSTA is not recommended in these situations.

## DOSAGE AND ADMINISTRATION

- Recommended dosage regimen is 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Reconstitute, dilute and administer as an intravenous infusion only, over a period of 1 hour. (2.1)
- Consider administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions (2.2)

## DOSAGE FORMS AND STRENGTHS

Single-use vials of belimumab lyophilized powder:

- 120 mg per vial (3)
- 400 mg per vial (3)

## CONTRAINDICATIONS

Previous anaphylaxis to belimumab. (4)

## WARNINGS AND PRECAUTIONS

- Mortality:** There were more deaths reported with BENLYSTA than with placebo during the controlled period of clinical trials. (5.1)
- Serious Infections:** Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including BENLYSTA. Use with caution in patients with chronic infections. Consider interrupting BENLYSTA therapy if patients develop a new infection during BENLYSTA treatment. (5.2)
- Hypersensitivity Reactions, Including Anaphylaxis:** Serious reactions have been reported. BENLYSTA should be administered by healthcare providers prepared to manage anaphylaxis. Monitor patients during and for an appropriate period of time after administration of BENLYSTA. (2.2, 5.4)
- Depression:** Depression and suicidality have been reported in BENLYSTA studies. Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or other mood changes. (5.6)
- Immunization:** Live vaccines should not be given concurrently with BENLYSTA. (5.7)

## ADVERSE REACTIONS

Common adverse reactions (≥5%) in clinical trials were: nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Human Genome Sciences, Inc. at 1-877-423-6597 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

## USE IN SPECIFIC POPULATIONS

- Pregnancy:** Registry available. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: March 2011

## FULL PRESCRIBING INFORMATION: CONTENTS\*

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

BENLYSTA® (belimumab) is indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

#### *Limitations of Use*

The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of BENLYSTA is not recommended in these situations.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosage Schedule

BENLYSTA is for intravenous infusion **only** and must be reconstituted and diluted prior to administration [see *Dosage and Administration* 2.3]. Do not administer as an intravenous push or bolus.

The recommended dosage regimen is 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Reconstitute, dilute and administer as an intravenous infusion only, over a period of 1 hour. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a serious hypersensitivity reaction [see *Contraindications* (4), *Warnings and Precautions* (5.4)].

#### 2.2 Premedication Recommendations

Prior to dosing with BENLYSTA, consider administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions. [see *Warnings and Precautions* (5.4.5.5) and *Adverse Reactions* (6.1)].

#### 2.3 Preparation of Solutions

BENLYSTA is provided as a lyophilized powder in a single-use vial for intravenous infusion only and should be reconstituted and diluted by a healthcare professional using aseptic technique as follows:

##### Reconstitution Instructions

1. Remove BENLYSTA from the refrigerator and allow to stand 10 to 15 minutes for the vial to reach room temperature.
2. Reconstitute the BENLYSTA powder with Sterile Water for Injection, USP, as follows. The reconstituted solution will contain a concentration of 80 mg/mL belimumab.
  - Reconstitute the 120 mg vial with 1.5 mL Sterile Water for Injection, USP.
  - Reconstitute the 400 mg vial with 4.8 mL Sterile Water for Injection, USP.
3. The stream of sterile water should be directed toward the side of the vial to minimize foaming. Gently swirl the vial for 60 seconds. Allow the vial to sit at room temperature during reconstitution, gently swirling the vial for 60 seconds every 5 minutes until the powder is dissolved. *Do not shake*. Reconstitution is typically complete within 10 to 15 minutes after the sterile water has been added, but it may take up to 30 minutes. Protect

- the reconstituted solution from sunlight.
- If a mechanical reconstitution device (swirler) is used to reconstitute BENLYSTA, it should not exceed 500 rpm and the vial swirled for no longer than 30 minutes.
  - Once reconstitution is complete, the solution should be opalescent and colorless to pale yellow, and without particles. Small air bubbles, however, are expected and acceptable.

#### **Dilution Instructions**

- Dextrose intravenous solutions are incompatible with BENLYSTA. BENLYSTA should only be diluted in 0.9% Sodium Chloride Injection, USP. Dilute the reconstituted product to 250 mL in 0.9% Sodium Chloride Injection, USP (normal saline) for intravenous infusion. From a 250-mL infusion bag or bottle of normal saline, withdraw and discard a volume equal to the volume of the reconstituted solution of BENLYSTA required for the patient's dose. Then add the required volume of the reconstituted solution of BENLYSTA into the infusion bag or bottle. Gently invert the bag or bottle to mix the solution. Any unused solution in the vials must be discarded.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the solution if any particulate matter or discoloration is observed.
- The reconstituted solution of BENLYSTA, if not used immediately, should be stored protected from direct sunlight and refrigerated at 2° to 8°C (36° to 46°F). Solutions of BENLYSTA diluted in normal saline may be stored at 2° to 8°C (36° to 46°F) or room temperature. The total time from reconstitution of BENLYSTA to completion of infusion should not exceed 8 hours.
- No incompatibilities between BENLYSTA and polyvinylchloride or polyolefin bags have been observed.

#### **2.4 Administration Instructions**

- The diluted solution of BENLYSTA should be administered by intravenous infusion only, over a period of 1 hour.
- BENLYSTA should be administered by healthcare providers prepared to manage anaphylaxis. [see *Warnings and Precautions* (5.4)]
- BENLYSTA should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of BENLYSTA with other agents.

#### **3 DOSAGE FORMS AND STRENGTHS**

Single-use vials of belimumab lyophilized powder for injection:

- 120 mg per vial
- 400 mg per vial

#### **4 CONTRAINDICATIONS**

BENLYSTA is contraindicated in patients who have had anaphylaxis with belimumab.

#### **5 WARNINGS AND PRECAUTIONS**

##### **5.1 Mortality**

There were more deaths reported with BENLYSTA than with placebo during the controlled period of the clinical trials. Out of 2133 patients in 3 clinical trials, a total of 14 deaths occurred

during the placebo-controlled, double-blind treatment periods: 3/675 (0.4%), 5/673 (0.7%), 0/111 (0%), and 6/674 (0.9%) deaths in the placebo, BENLYSTA 1 mg/kg, BENLYSTA 4 mg/kg, and BENLYSTA 10 mg/kg groups, respectively. No single cause of death predominated. Etiologies included infection, cardiovascular disease and suicide.

## 5.2 Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including BENLYSTA. Physicians should exercise caution when considering the use of BENLYSTA in patients with chronic infections. Patients receiving any therapy for chronic infection should not begin therapy with BENLYSTA. Consider interrupting BENLYSTA therapy in patients who develop a new infection while undergoing treatment with BENLYSTA and monitor these patients closely.

In the controlled clinical trials, the overall incidence of infections was 71% in patients treated with BENLYSTA compared with 67% in patients who received placebo. The most frequent infections (>5% of patients receiving BENLYSTA) were upper respiratory tract infection, urinary tract infection, nasopharyngitis, sinusitis, bronchitis, and influenza. Serious infections occurred in 6.0% of patients treated with BENLYSTA and in 5.2% of patients who received placebo. The most frequent serious infections included pneumonia, urinary tract infection, cellulitis, and bronchitis. Infections leading to discontinuation of treatment occurred in 0.7% of patients receiving BENLYSTA and 1.0% of patients receiving placebo. Infections resulting in death occurred in 0.3% (4/1458) of patients treated with BENLYSTA and in 0.1% (1/675) of patients receiving placebo.

## 5.3 Malignancy

The impact of treatment with BENLYSTA on the development of malignancies is not known. In the controlled clinical trials, malignancies (including non-melanoma skin cancers) were reported in 0.4% of patients receiving BENLYSTA and 0.4% of patients receiving placebo. In the controlled clinical trials, malignancies, excluding non-melanoma skin cancers, were observed in 0.2% (3/1458) and 0.3% (2/675) of patients receiving BENLYSTA and placebo, respectively. As with other immunomodulating agents, the mechanism of action of BENLYSTA could increase the risk for the development of malignancies.

## 5.4 Hypersensitivity Reactions, Including Anaphylaxis

In the controlled clinical trials, hypersensitivity reactions (occurring on the same day of infusion) were reported in 13% (191/1458) of patients receiving BENLYSTA and 11% (76/675) of patients receiving placebo. Anaphylaxis was observed in 0.6% (9/1458) of patients receiving BENLYSTA and 0.4% (3/675) of patients receiving placebo. Manifestations included hypotension, angioedema, urticaria or other rash, pruritus, and dyspnea. Due to overlap in signs and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases [see Warnings and Precautions (5.5)]. Some patients (13%) received premedication, which may have mitigated or masked a hypersensitivity response; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of hypersensitivity reactions.

BENLYSTA should be administered by healthcare providers prepared to manage anaphylaxis. In the event of a serious reaction, administration of BENLYSTA must be discontinued immediately and appropriate medical therapy administered. Patients should be monitored during and for an appropriate period of time after administration of BENLYSTA. Patients should be informed of the signs and symptoms of a hypersensitivity reaction and instructed to seek immediate medical care should a reaction occur.

## 5.5 Infusion Reactions

In the controlled clinical trials, adverse events associated with the infusion (occurring on the same day of the infusion) were reported in 17% (251/1458) of patients receiving BENLYSTA and 15% (99/675) of patients receiving placebo. Serious infusion reactions (excluding hypersensitivity reactions) were reported in 0.5% of patients receiving BENLYSTA and 0.4% of patients receiving placebo and included bradycardia, myalgia, headache, rash, urticaria, and hypotension. The most common infusion reactions ( $\geq 3\%$  of patients receiving BENLYSTA) were headache, nausea, and skin reactions. Due to overlap in signs and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases [see *Warnings and Precautions* (5.4)]. Some patients (13%) received premedication, which may have mitigated or masked an infusion reaction; however there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion reactions [see *Adverse Reactions* (6.1)].

BENLYSTA should be administered by healthcare providers prepared to manage infusion reactions. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. Healthcare providers should be aware of the risk of hypersensitivity reactions, which may present as infusion reactions, and monitor patients closely.

## 5.6 Depression

In the controlled clinical trials, psychiatric events were reported more frequently with BENLYSTA (16%) than with placebo (12%), related primarily to depression-related events (6.3% BENLYSTA and 4.7% placebo), insomnia (6.0% BENLYSTA and 5.3% placebo), and anxiety (3.9% BENLYSTA and 2.8% placebo). Serious psychiatric events were reported in 0.8% of patients receiving BENLYSTA (0.6% and 1.2% with 1 and 10 mg/kg, respectively) and 0.4% of patients receiving placebo. Serious depression was reported in 0.4% (6/1458) of patients receiving BENLYSTA and 0.1% (1/675) of patients receiving placebo. Two suicides (0.1%) were reported in patients receiving BENLYSTA. The majority of patients who reported serious depression or suicidal behavior had a history of depression or other serious psychiatric disorders and most were receiving psychoactive medications. It is unknown if BENLYSTA treatment is associated with increased risk for these events.

Patients receiving BENLYSTA should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts, or other mood changes.

## 5.7 Immunization

Live vaccines should not be given for 30 days before or concurrently with BENLYSTA as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving BENLYSTA or the effect of

BENLYSTA on new immunizations. Because of its mechanism of action, BENLYSTA may interfere with the response to immunizations.

### **5.8 Concomitant Use with Other Biologic Therapies or Intravenous Cyclophosphamide**

BENLYSTA has not been studied in combination with other biologic therapies, including B-cell targeted therapies, or intravenous cyclophosphamide. Therefore, use of BENLYSTA is not recommended in combination with biologic therapies or intravenous cyclophosphamide.

## **6 ADVERSE REACTIONS**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following have been observed with BENLYSTA and are discussed in detail in the Warnings and Precautions section:

- **Mortality** [see *Warnings and Precautions (5.1)*]
- **Serious Infections** [see *Warnings and Precautions (5.2)*]
- **Malignancy** [see *Warnings and Precautions (5.3)*]
- **Hypersensitivity Reactions, Including Anaphylaxis** [see *Warnings and Precautions (5.4)*]
- **Infusion reactions** [see *Warnings and Precautions (5.5)*]
- **Depression** [see *Warnings and Precautions (5.6)*]

### **6.1 Clinical Trials Experience**

The data described below reflect exposure to BENLYSTA plus standard of care compared with placebo plus standard of care in 2133 patients in 3 controlled studies. Patients received BENLYSTA at doses of 1 mg/kg (N=673), 4 mg/kg (N=111; Trial 1 only), or 10 mg/kg (N=674) or placebo (N=675) intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days. In two of the studies (Trial 1 and Trial 3), treatment was given for 48 weeks, while in the other study (Trial 2) treatment was given for 72 weeks [see *Clinical Studies (14)*]. Because there was no apparent dose-related increase in the majority of adverse events observed with BENLYSTA, the safety data summarized below are presented for the 3 doses pooled, unless otherwise indicated; the adverse reaction table displays the results for the recommended dose of 10 mg/kg compared with placebo.

The population had a mean age of 39 (range 18-75), 94% were female, and 52% were Caucasian. In these trials, 93% of patients treated with BENLYSTA reported an adverse reaction compared with 92% treated with placebo.

The most common serious adverse reactions were serious infections (6.0% and 5.2% in the groups receiving BENLYSTA and placebo, respectively) [see *Warnings and Precautions (5.2)*].

The most commonly-reported adverse reactions, occurring in ≥5% of patients in clinical trials were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis.

The proportion of patients who discontinued treatment due to any adverse reaction during the controlled clinical trials was 6.2% for patients receiving BENLYSTA and 7.1% for patients receiving placebo. The most common adverse reactions resulting in discontinuation of treatment ( $\geq 1\%$  of patients receiving BENLYSTA or placebo) were infusion reactions (1.6% BENLYSTA and 0.9% placebo), lupus nephritis (0.7% BENLYSTA and 1.2% placebo), and infections (0.7% BENLYSTA and 1.0% placebo).

Table 1 lists adverse reactions, regardless of causality, occurring in at least 3% of patients with SLE who received BENLYSTA 10 mg/kg and at an incidence at least 1% greater than that observed with placebo in the 3 controlled studies.

**Table 1 Incidence of Adverse Reactions Occurring in at Least 3% of Patients Treated With BENLYSTA 10 mg/kg Plus Standard of Care and at Least 1% More Frequently Than in Patients Receiving Placebo plus Standard of Care in 3 Controlled SLE Studies**

Preferred Term	BENLYSTA 10 mg/kg + Standard of Care (n = 674) %	Placebo + Standard of Care (n = 675) %
Nausea	15	12
Diarrhea	12	9
Pyrexia	10	8
Nasopharyngitis	9	7
Bronchitis	9	5
Insomnia	7	5
Pain in extremity	6	4
Depression	5	4
Migraine	5	4
Pharyngitis	5	3
Cystitis	4	3
Leukopenia	4	2
Gastroenteritis viral	3	1

## 6.2 Immunogenicity

In Trials 2 and 3, anti-belimumab antibodies were detected in 4 of 563 (0.7%) patients receiving BENLYSTA 10 mg/kg and in 27 of 559 (4.8%) patients receiving BENLYSTA 1 mg/kg. The reported frequency for the group receiving 10 mg/kg may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentrations. Neutralizing antibodies were detected in 3 patients receiving BENLYSTA 1 mg/kg. Three patients with anti-belimumab antibodies experienced mild infusion reactions of nausea, erythematous rash, pruritus, eyelid edema, headache, and dyspnea; none of the reactions was life-threatening. The clinical relevance of the presence of anti-belimumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to belimumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology,

sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to belimumab with the incidence of antibodies to other products may be misleading.

## 7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with BENLYSTA. In clinical trials of patients with SLE, BENLYSTA was administered concomitantly with other drugs, including corticosteroids, antimalarials, immunomodulatory and immunosuppressive agents (including azathioprine, methotrexate, and mycophenolate), angiotensin pathway antihypertensives, HMG-CoA reductase inhibitors (statins), and NSAIDs without evidence of a clinically meaningful effect of these concomitant medications on belimumab pharmacokinetics. The effect of belimumab on the pharmacokinetics of other drugs has not been evaluated [see *Pharmacokinetics 12.3*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled clinical studies using BENLYSTA in pregnant women. Immunoglobulin G (IgG) antibodies, including BENLYSTA, can cross the placenta. Because animal reproduction studies are not always predictive of human response, BENLYSTA should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Women of childbearing potential should use adequate contraception during treatment with BENLYSTA and for at least 4 months after the final treatment.

Nonclinical reproductive studies have been performed in pregnant cynomolgus monkeys receiving belimumab at doses of 0, 5 and 150 mg/kg by intravenous infusion (the high dose was approximately 9 times the anticipated maximum human exposure) every 2 weeks from gestation day 20 to 150. Belimumab was shown to cross the placenta. Belimumab was not associated with direct or indirect teratogenicity under the conditions tested. Fetal deaths were observed in 14%, 24% and 15% of pregnant females in the 0, 5 and 150 mg/kg groups, respectively. Infant deaths occurred with an incidence of 0%, 8% and 5%. The cause of fetal and infant deaths is not known. The relevance of these findings to humans is not known. Other treatment-related findings were limited to the expected reversible reduction of B cells in both dams and infants and reversible reduction of IgM in infant monkeys. B-cell numbers recovered after the cessation of belimumab treatment by about 1 year post-partum in adult monkeys and by 3 months of age in infant monkeys. IgM levels in infants exposed to belimumab in utero recovered by 6 months of age.

Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to BENLYSTA, a pregnancy registry has been established. Healthcare professionals are encouraged to register patients and pregnant women are encouraged to enroll themselves by calling 1-877-681-6296.

### 8.3 Nursing Mothers

It is not known whether BENLYSTA is excreted in human milk or absorbed systemically after ingestion. However, belimumab was excreted into the milk of cynomolgus monkeys. Because



maternal antibodies are excreted in human breast milk, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of breastfeeding to the infant and the importance of the drug to the mother.

#### **8.4 Pediatric Use**

Safety and effectiveness of BENLYSTA have not been established in children.

#### **8.5 Geriatric Use**

Clinical studies of BENLYSTA did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects. Use with caution in elderly patients.

#### **8.6 Race**

In Trial 2 and Trial 3, response rates for the primary endpoint were lower for black subjects in the BENLYSTA group relative to black subjects in the placebo group [see *Clinical Studies* (14)]. Use with caution in black/African-American patients.

### **10 OVERDOSAGE**

There is no clinical experience with overdosage of BENLYSTA. Two doses of up to 20 mg/kg have been given by intravenous infusion to humans with no increase in incidence or severity of adverse reactions compared with doses of 1, 4, or 10 mg/kg.

### **11 DESCRIPTION**

BENLYSTA (belimumab) is a human IgG1 $\lambda$  monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab has a molecular weight of approximately 147 kDa. Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

BENLYSTA is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for intravenous infusion. Upon reconstitution with Sterile Water for Injection, USP, [see *Dosage and Administration* (2.3)] each single-use vial delivers 80 mg/mL belimumab in 0.16 mg/mL citric acid, 0.4 mg/mL polysorbate 80, 2.7 mg/mL sodium citrate, and 80 mg/mL sucrose, with a pH of 6.5.

### **12 CLINICAL PHARMACOLOGY**

#### **12.1 Mechanism of Action**

BENLYSTA is a BLyS-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells. BENLYSTA does not bind B cells directly, but by binding BLyS, BENLYSTA inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

#### **12.2 Pharmacodynamics**

In Trial 1 and Trial 2 in which B cells were measured, treatment with BENLYSTA significantly reduced circulating CD19+, CD20+, naïve, and activated B cells, plasmacytoid cells, and the SLE B-cell subset at Week 52. Reductions in naïve and the SLE B-cell subset were observed as early as Week 8 and were sustained to Week 52. Memory cells increased initially and slowly.

declined toward baseline levels by Week 52. The clinical relevance of these effects on B cells has not been established.

Treatment with BENLYSTA led to reductions in IgG and anti-dsDNA, and increases in complement (C3 and C4). These changes were observed as early as Week 8 and were sustained through Week 52. The clinical relevance of normalizing these biomarkers has not been definitively established.

### 12.3 Pharmacokinetics

The pharmacokinetic parameters displayed in Table 2 are based on population parameter estimates which are specific to the 563 patients who received belimumab 10 mg/kg in Trials 2 and 3 [see *Clinical Studies* (14)].

Table 2. Population Pharmacokinetic Parameters in Patients with SLE after Intravenous Infusion of BENLYSTA 10 mg/kg<sup>1</sup>

Pharmacokinetic Parameter	Population Estimates (n = 563)
Peak concentration ( $C_{max}$ , $\mu\text{g/mL}$ )	313
Area under the curve ( $AUC_{0-\infty}$ , $\text{day} \cdot \mu\text{g/mL}$ )	3,083
Distribution half-life ( $t_{1/2}$ , days)	1.75
Terminal half-life ( $t_{1/2}$ , days)	19.4
Systemic clearance ( $CL$ , $\text{mL/day}$ )	215
Volume of distribution ( $V_{ss}$ , L)	5.29

Intravenous infusions were administered at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

**Drug Interactions:** No formal drug interaction studies have been conducted with belimumab. Concomitant use of mycophenolate, azathioprine, methotrexate, antimalarials, NSAIDs, aspirin, and HMG-CoA reductase inhibitors did not significantly influence belimumab pharmacokinetics. Coadministration of steroids and angiotensin-converting enzyme (ACE) inhibitors resulted in an increase of systemic clearance of belimumab that was not clinically significant because the magnitude was well within the range of normal variability of clearance. The effect of belimumab on the pharmacokinetics of other drugs has not been evaluated.

#### Special Populations:

The following information is based on the population pharmacokinetic analysis.

**Age:** Age did not significantly influence belimumab pharmacokinetics in the study population, where the majority of subjects (70%) were between 18 and 45 years of age. No pharmacokinetic data are available in pediatric patients. Limited pharmacokinetic data are available for elderly patients as only 1.4% of the subjects included in the pharmacokinetic analysis were 65 years of age or older [see *Use in Specific Populations* (8.5)].

**Gender:** Gender did not significantly influence belimumab pharmacokinetics in the largely (94%) female study population.

*Race:* Race did not significantly influence belimumab pharmacokinetics. The racial distribution was 53% white/Caucasian, 16% Asian, 16% Alaska native/American Indian, and 14% black/African American.

*Renal Impairment:* No formal studies were conducted to examine the effects of renal impairment on the pharmacokinetics of belimumab. Belimumab has been studied in a limited number of patients with SLE and renal impairment (261 subjects with moderate renal impairment, creatinine clearance  $\geq 30$  and  $< 60$  mL/min; 14 subjects with severe renal impairment, creatinine clearance  $\geq 15$  and  $< 30$  mL/min). Although increases in creatinine clearance and proteinuria ( $> 2$  g/day) increased belimumab clearance, these effects were within the expected range of variability. Therefore, dosage adjustment in patients with renal impairment is not recommended.

*Hepatic Impairment:* No formal studies were conducted to examine the effects of hepatic impairment on the pharmacokinetics of belimumab. Belimumab has not been studied in patients with severe hepatic impairment. Baseline ALT and AST levels did not significantly influence belimumab pharmacokinetics.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of belimumab. The mutagenic potential of belimumab was not evaluated.

Effects on male and female fertility have not been directly evaluated in animal studies.

## 14 CLINICAL STUDIES

The safety and effectiveness of BENLYSTA were evaluated in three randomized, double-blind, placebo-controlled studies involving 2133 patients with SLE according to the American College of Rheumatology criteria (Trial 1, 2, and 3). Patients with severe active lupus nephritis and severe active CNS lupus were excluded. Patients were on a stable standard of care SLE treatment regimen comprising any of the following (alone or in combination): corticosteroids, antimalarials, NSAIDs, and immunosuppressives. Use of other biologics and intravenous cyclophosphamide were not permitted.

### *Trial 1: BENLYSTA 1 mg/kg, 4 mg/kg, 10 mg/kg*

Trial 1 enrolled 449 patients and evaluated doses of 1, 4, and 10 mg/kg BENLYSTA plus standard of care compared with placebo plus standard of care over 52 weeks in patients with SLE. Patients had to have a SELENA-SLEDAI score of  $\geq 4$  at baseline and a history of autoantibodies (anti-nuclear antibody (ANA) and/or anti-double-stranded DNA (anti-dsDNA), but 28% of the population was autoantibody negative at baseline. The co-primary endpoints were percent change in SELENA-SLEDAI score at Week 24 and time to first flare over 52 weeks. No significant differences between any of the BENLYSTA groups and the placebo group were observed. Exploratory analysis of this study identified a subgroup of patients (72%), who were autoantibody positive, in whom BENLYSTA appeared to offer benefit. The results of

this study informed the design of Trials 2 and 3 and led to the selection of a target population and indication that is limited to autoantibody-positive SLE patients.

***Trials 2 and 3: BENLYSTA 1 mg/kg and 10 mg/kg***

Trials 2 and 3 were randomized, double-blind, placebo-controlled trials in patients with SLE that were similar in design except duration - Trial 2 was 76 weeks duration and Trial 3 was 52 weeks duration. Eligible patients had active SLE disease, defined as a SELENA-SLEDAI score  $\geq 6$ , and positive autoantibody test results at screening. Patients were excluded from the study if they had ever received treatment with a B-cell targeted agent or if they were currently receiving other biologic agents. Intravenous cyclophosphamide was not permitted within the previous 6 months or during study. Trial 2 was conducted primarily in North America and Europe. Trial 3 was conducted in South America, Eastern Europe, Asia, and Australia.

Baseline concomitant medications included corticosteroids (Trial 2: 76%, Trial 3: 96%), immunosuppressives (Trial 2: 56%, Trial 3: 42%; including azathioprine, methotrexate and mycophenolate), and antimalarials (Trial 2: 63%, Trial 3: 67%). Most patients ( $>70\%$ ) were receiving 2 or more classes of SLE medications.

In Trial 2 and Trial 3, more than 50% of patients had 3 or more active organ systems at baseline. The most common active organ systems at baseline based on SELENA SLEDAI were mucocutaneous (82% in both studies); immunology (Trial 2: 74%, Trial 3: 85%); and musculoskeletal (Trial 2: 73%, Trial 3: 59%). Less than 16% of patients had some degree of renal activity and less than 7% of patients had activity in the vascular, cardio-respiratory, or CNS systems.

At screening, patients were stratified by disease severity based on their SELENA-SLEDAI score ( $\leq 9$  vs  $\geq 10$ ), proteinuria level ( $<2$  g/24 hr vs  $\geq 2$  g/24 hr), and race (African or Indigenous-American descent vs. other), and then randomly assigned to receive BENLYSTA 1 mg/kg, BENLYSTA 10 mg/kg, or placebo in addition to standard of care. The patients were administered study medication intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days for 48 weeks in Trial 3 and for 72 weeks in Trial 2.

The primary efficacy endpoint was a composite endpoint (SLE Responder Index or SRI) that defined response as meeting each of the following criteria at Week 52 compared with baseline:

- $\geq 4$ -point reduction in the SELENA-SLEDAI score, and
- no new British Isles Lupus Assessment Group (BILAG) A organ domain score or 2 new BILAG B organ domain scores, and
- no worsening ( $<0.30$ -point increase) in Physician's Global Assessment (PGA) score.

The SRI uses the SELENA-SLEDAI score as an objective measure of reduction in global disease activity; the BILAG index to ensure no significant worsening in any specific organ system; and the PGA to ensure that improvements in disease activity are not accompanied by worsening of the patient's condition overall.

In both Trials 2 and 3, the proportion of SLE patients achieving an SRI response, as defined for the primary endpoint, was significantly higher in the BENLYSTA 10 mg/kg group than in the

placebo group in both studies. The effect on the SRI was not consistently significantly different for the BENLYSTA 1mg/kg group relative to placebo in both trials. The 1 mg/kg dose is not recommended. The trends in comparisons between the treatment groups for the rates of response for the individual components of the endpoint were generally consistent with that of the SRI (Table 3). At Week 76 in Trial 2, the SRI response rate with BENLYSTA 10 mg/kg was not significantly different from that of placebo (39% and 32%, respectively).

**Table 3. Clinical Response Rate in Patients with SLE After 52 Weeks of Treatment**

Response <sup>1</sup>	Trial 2			Trial 3		
	Placebo + Standard of Care (n = 275)	BENLYSTA 1 mg/kg + Standard of Care <sup>2</sup> (n = 271)	BENLYSTA 10 mg/kg + Standard of Care (n = 273)	Placebo + Standard of Care (n = 287)	BENLYSTA 1 mg/kg + Standard of Care <sup>2</sup> (n = 288)	BENLYSTA 10 mg/kg + Standard of Care (n = 290)
SLE Responder Index	34%	41%  (p = 0.104)	43%  (p = 0.021)	44%	51%  (p = 0.013)	58%  (p < 0.001)
Odds Ratio (95% CI) vs. placebo		1.3 (0.9, 1.9)	1.5 (1.1, 2.2)		1.6 (1.1, 2.2)	1.8 (1.3, 2.6)
<b>Components of SLE Responder Index</b>						
Percent of patients with reduction in SELENA- SLEDAI $\geq 4$	36%	43%	47%	46%	53%	58%
Percent of patients with no worsening by BILAG index	65%	75%	69%	73%	79%	81%
Percent of patients with no worsening by PGA	63%	73%	69%	69%	79%	80%

<sup>1</sup>Patients dropping out of the study early or experiencing certain increases in background medication were considered as failures in these analyses. In both studies, a higher proportion of placebo patients were considered as failures for this reason as compared to the BENLYSTA groups.

<sup>2</sup>The 1 mg/kg dose is not recommended.

The reduction in disease activity seen in the SRI was related primarily to improvement in the most commonly involved organ systems namely, mucocutaneous, musculoskeletal, and immunology.

#### *Effect in Black/African-American Patients*

Exploratory sub-group analyses of SRI response rate in patients of black race were performed. In Trial 2 and Trial 3 combined, the SRI response rate in black patients (N=148) in the BENLYSTA groups was less than that in the placebo group (22/50 or 44% for placebo, 15/48 or 31% for BENLYSTA 1 mg/kg, and 18/50 or 36% for BENLYSTA 10 mg/kg). In Trial 1, black patients (N=106) in the BENLYSTA groups did not appear to have a different response than the

rest of the study population. Although no definitive conclusions can be drawn from these subgroup analyses, caution should be used when considering BENLYSTA treatment in black/African-American SLE patients.

#### *Effect on Concomitant Steroid Treatment:*

In Trial 2 and Trial 3, 46% and 69% of patients, respectively, were receiving prednisone at doses > 7.5 mg/day at baseline. The proportion of patients able to reduce their average prednisone dose by at least 25% to ≤7.5 mg/day during Weeks 40 through 52 was not consistently significantly different for BENLYSTA relative to placebo in both trials. In Trial 2, 17% of patients receiving BENLYSTA 10 mg/kg and 19% of patients receiving BENLYSTA 1 mg/kg achieved this level of steroid reduction compared with 13% of patients receiving placebo. In Trial 3, 19%, 21%, and 12% of patients receiving BENLYSTA 10 mg/kg, BENLYSTA 1 mg/kg, and placebo, respectively, achieved this level of steroid reduction.

#### *Effect on Severe SLE Flares:*

The probability of experiencing a severe SLE flare, as defined by a modification of the SELENA-SLEDAI score of >12, was calculated for both Trials 2 and 3. The proportion of patients having at least 1 severe flare over 52 weeks was not consistently significantly different for BENLYSTA relative to placebo in both trials. In Trial 2, 18% of patients receiving BENLYSTA 10 mg/kg and 16% of patients receiving BENLYSTA 1 mg/kg had a severe flare compared with 24% of patients receiving placebo. In Trial 3, 14%, 18%, and 23% of patients receiving BENLYSTA 10 mg/kg, BENLYSTA 1 mg/kg and placebo, respectively, had a severe flare.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

BENLYSTA is a sterile, preservative-free lyophilized powder for reconstitution, dilution, and intravenous infusion provided in single-use glass vials with a latex-free rubber stopper and a flip-off seal. Each 5-mL vial contains 120 mg of belimumab. Each 20-mL vial contains 400 mg of belimumab.

BENLYSTA is supplied as follows:

120 mg belimumab in a 5-mL single-use vial	NDC 49401-101-01
400 mg belimumab in a 20-mL single-use vial	NDC 49401-102-01

Store vials of BENLYSTA refrigerated between 2° to 8°C (36° to 46°F). Vials should be protected from light and stored in the original carton until use. *Do not freeze.* Avoid exposure to heat. Do not use beyond the expiration date.

## **17 PATIENT COUNSELING INFORMATION**

*See Medication Guide.*

### **17.1 Advice for the Patient**

Patients should be given the Medication Guide for BENLYSTA and provided an opportunity to read it prior to each treatment session. It is important that the patient's overall health be assessed at each infusion visit and any questions resulting from the patient's reading of the Medication Guide be discussed.

**Mortality:** Patients should be advised that more patients receiving BENLYSTA in the main clinical trials died than did patients receiving placebo treatment [see *Warnings and Precautions* (5.1)].

**Serious Infections:** Patients should be advised that BENLYSTA may decrease their ability to fight infections. Patients should be asked if they have a history of chronic infections and if they are currently on any therapy for an infection [see *Warnings and Precautions* (5.2)]. Patients should be instructed to tell their healthcare provider if they develop signs or symptoms of an infection.

**Hypersensitivity/Anaphylactic and Infusion Reactions:** Educate patients on the signs and symptoms of anaphylaxis, including wheezing, difficulty breathing, peri-oral or lingual edema, and rash. Patients should be instructed to immediately tell their healthcare provider if they experience symptoms of an allergic reaction during or after the administration of BENLYSTA [see *Warnings and Precautions* (5.4, 5.5)].

**Depression:** Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or other mood changes. [see *Warnings and Precautions* (5.6)].

**Immunizations:** Patients should be informed that they should not receive live vaccines while taking BENLYSTA. Response to vaccinations could be impaired by BENLYSTA [see *Warnings and Precautions* (5.7)].

**Pregnancy and Nursing Mothers:** Patients should be informed that BENLYSTA has not been studied in pregnant women or nursing mothers so the effects of BENLYSTA on pregnant women or nursing infants are not known. Patients should be instructed to tell their healthcare provider if they are pregnant, become pregnant, or are thinking about becoming pregnant [see *Use in Specific Populations* (8.1)]. Patients should be instructed to tell their healthcare provider if they plan to breastfeed their infant [see *Use in Specific Populations* (8.3)].

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## MEDICATION GUIDE

### **BENLYSTA®** (ben-LIST-ah) (belimumab)

#### **Injection for intravenous use**

Read this Medication Guide before you start receiving BENLYSTA and before each treatment. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

#### **What is the most important information I should know about BENLYSTA?**

BENLYSTA can cause serious side effects. Some of these side effects may cause death. It is not known if BENLYSTA causes these serious side effects. Tell your healthcare provider right away if you have any of the symptoms listed below while receiving BENLYSTA.

##### **1. Infections.** Symptoms of an infection can include:

- fever
- chills
- pain or burning with urination
- urinating often
- bloody diarrhea
- coughing up mucus

##### **2. Heart Problems.** Symptoms of heart problems can include:

- chest discomfort or pain
- shortness of breath
- cold sweats
- nausea
- dizziness
- discomfort in other areas of the upper body

##### **3. Mental health problems and suicide.** Symptoms of mental health problems can include:

- thoughts of suicide or dying
- attempt to commit suicide
- trouble sleeping (insomnia)
- new or worse anxiety
- new or worse depression
- acting on dangerous impulses
- other unusual changes in your behavior or mood
- thoughts of hurting yourself or others

37 **What is BENLYSTA?**

38 BENLYSTA is a prescription medicine used to treat adults with active systemic lupus  
39 erythematosus (SLE or lupus) who are receiving other lupus medicines.

40 BENLYSTA contains *belimumab* which is in a group of medicines called *monoclonal*  
41 *antibodies*. Lupus is a disease of the immune system (the body system that fights infection).  
42 People with active lupus often have high levels of a certain protein in their blood. BENLYSTA  
43 binds to and limits the activity of the protein. When given together with other medicines for  
44 lupus, BENLYSTA decreases lupus disease activity more than other lupus medicines alone.

- 45 • It is not known if BENLYSTA is safe and effective in people with severe active lupus  
46 nephritis or severe active central nervous system lupus.
- 47 • It is not known if BENLYSTA is safe and effective in children.

48 **Who should not receive BENLYSTA?**

49 **Do not receive BENLYSTA if you:**

- 50 • are allergic to belimumab or any of the ingredients in BENLYSTA. See the end of this  
51 Medication Guide for a complete list of ingredients in BENLYSTA.

52 **What should I tell my healthcare provider before receiving BENLYSTA?**

53 Before you receive BENLYSTA, tell your healthcare provider if you:

- 54 • think you have an infection or have infections that keep coming back. You should not  
55 receive BENLYSTA if you have an infection unless your healthcare provider tells you to.  
56 See **"What is the most important information I should know about BENLYSTA."**
- 57 • have or have had mental health problems such as depression or thoughts of suicide
- 58 • have recently received a vaccination or if you think you may need a vaccination. If you  
59 are receiving BENLYSTA, you should not receive live vaccines.
- 60 • are receiving other biologic medicines, monoclonal antibodies or IV infusions of  
61 cyclophosphamide (Cytosan®)
- 62 • have or have had any type of cancer
- 63 • have any other medical conditions
- 64 • are pregnant or plan to become pregnant. It is not known if BENLYSTA will harm your  
65 unborn baby. Tell your healthcare provider if you become pregnant during your treatment  
66 with BENLYSTA.
- 67 • If you become pregnant while receiving BENLYSTA, talk to your healthcare provider  
68 about enrolling in the BENLYSTA Pregnancy Registry. You can enroll in this  
69 registry by calling 1-877-681-6296. The purpose of this registry is to monitor the  
70 health of you and your baby.

- 71 • are breastfeeding or plan to breastfeed. It is not known if BENLYSTA passes into your  
72 breast milk. You and your healthcare provider should decide if you will receive  
73 BENLYSTA or breastfeed. You should not do both.

74 **Tell your healthcare provider about all the medicines you take, including prescription and**  
75 **non-prescription medicines, vitamins, and herbal supplements.**

76 **Know the medicines you take. Keep a list of your medicines with you to show to your**  
77 **healthcare provider and pharmacist when you get a new medicine.**

78 **How will I receive BENLYSTA?**

- 79 • You will be given BENLYSTA by a healthcare provider through a needle placed in a  
80 vein (IV infusion). It takes about 1 hour to give you the full dose of BENLYSTA.  
81 • Your healthcare provider will tell you how often you should receive BENLYSTA.  
82 • Your healthcare provider may give you medicines before you receive BENLYSTA to  
83 help reduce your chance of having a reaction. A healthcare provider will watch you  
84 closely while you are receiving BENLYSTA and after your infusion for signs of a  
85 reaction.

86 **What are the possible side effects of BENLYSTA?**

87 **BENLYSTA can cause serious side effects.**

88 • See "What is the most important information I should know about BENLYSTA?"

89 **1. Cancer.** BENLYSTA may reduce the activity of your immune system. Medicines that affect  
90 the immune system may increase your risk of certain cancers.

91 **2. Allergic (hypersensitivity) and infusion reactions.** Serious allergic or infusion reactions  
92 can happen on the day of or the day after receiving BENLYSTA. Symptoms of an allergic or  
93 infusion reaction may include:

- 94 • itching  
95 • swelling of the face, lips, mouth, tongue, or throat  
96 • trouble breathing  
97 • anxiousness  
98 • low blood pressure  
99 • dizziness or fainting  
100 • headache  
101 • nausea  
102 • skin rash, redness, or swelling

Your healthcare provider will watch you closely while you are receiving BENLYSTA and after your infusion for signs of a reaction.

**The most common side effects of BENLYSTA include:**

- nausea
- diarrhea
- fever
- stuffy or runny nose
- sore throat
- cough (bronchitis)
- trouble sleeping
- leg or arm pain
- headache (migraine)
- urinary tract infection
- decreased white blood cell count (leukopenia)
- vomiting
- stomach pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of BENLYSTA. For more information, ask your healthcare provider.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of BENLYSTA**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BENLYSTA for a condition for which it was not prescribed.

This Medication Guide summarizes the most important information about BENLYSTA. For more information about BENLYSTA, talk with your healthcare provider.

You can ask your healthcare provider or pharmacist for information about BENLYSTA that is written for healthcare professionals.

For more information about BENLYSTA, go to [www.BENLYSTA.com](http://www.BENLYSTA.com) or call 1-877-423-6597.

**What are the ingredients in BENLYSTA?**

**Active ingredient:** belimumab.

**Inactive ingredients:** citric acid, polysorbate 80, sodium citrate, sucrose.

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138  
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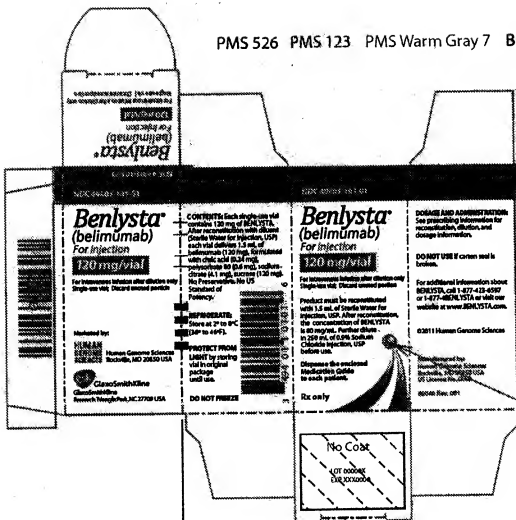
GlaxoSmithKline  
Research Triangle Park, NC 27709

148 This Medication Guide has been approved by the U.S. Food and Drug Administration.

149 Issued: March 2011

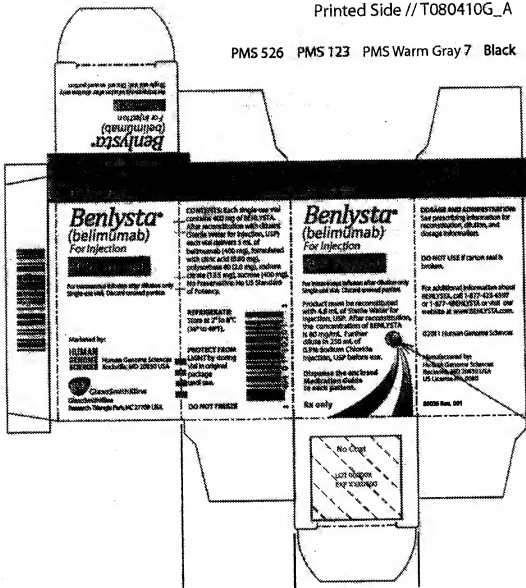
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PMS 526 PMS 123 PMS Warm Gray 7 B



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PMS 526 PMS 123 PMS Warm Gray 7 Black



**Benlysta<sup>®</sup>**  
(belimumab)

For Injection

**120 mg/vial**

For intravenous infusion after dilution only  
Single-use vial; Discard unused portion.

NDC 49401-101-01

See prescribing information for reconstitution, dilution, and dosage information.

**REFRIGERATE:** Store at 2° to 8°C (36° to 46°F). Protect from light by storing in original package until use.

Do Not Freeze

Human Genome Sciences  
Rockville, MD 20850 USA  
US License No. 0600

Rx only

80039 Rev. 001

**Benlysta<sup>®</sup>**  
(belimumab)

For Injection

**120 mg/vial**

For intravenous infusion after dilution only  
Single-use vial; Discard unused portion.

NDC 49401-102-01

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U.S. Patent No. 7,138,501

Application for Patent Term Extension

# **Attachment C**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BENLYSTA safely and effectively. See full prescribing information for BENLYSTA.

**BENLYSTA® (belimumab)**  
for injection, for intravenous use only  
Initial U.S. Approval: 2011

### INDICATIONS AND USAGE

BENLYSTA is a B-lymphocyte stimulator (BLyS)-specific inhibitor indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. (1, 14)

**Limitations of Use:** The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus (1). BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide (1). Use of BENLYSTA is not recommended in these situations.

### DOSAGE AND ADMINISTRATION

- Recommended dosage regimen is 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Reconstitute, dilute and administer as an intravenous infusion only, over a period of 1 hour. (2.1)
- Consider administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions (2.2)

### DOSAGE FORMS AND STRENGTHS

Single-use vials of belimumab lyophilized powder:

- 120 mg per vial (3)
- 400 mg per vial (3)

### CONTRAINDICATIONS

Previous anaphylaxis to belimumab. (4)

### WARNINGS AND PRECAUTIONS

- Mortality:** There were more deaths reported with BENLYSTA than with placebo during the controlled period of clinical trials. (5.1)
- Serious Infections:** Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including BENLYSTA. Use with caution in patients with chronic infections. Consider interrupting BENLYSTA therapy if patients develop a new infection during BENLYSTA treatment. (5.2)
- Hypersensitivity Reactions, Including Anaphylaxis:** Serious reactions have been reported. BENLYSTA should be administered by healthcare providers prepared to manage anaphylaxis. Monitor patients during and for an appropriate period of time after administration of BENLYSTA. (2.2, 5.4)
- Depression:** Depression and suicidality have been reported in BENLYSTA studies. Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or other mood changes. (5.6)
- Immunization:** Live vaccines should not be given concurrently with BENLYSTA. (5.7)

### ADVERSE REACTIONS

Common adverse reactions (≥5%) in clinical trials were: nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Human Genome Sciences, Inc. at 1-877-423-6597 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

- Pregnancy:** Registry available. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: March 2011

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

BENLYSTA® (belimumab) is indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

#### *Limitations of Use*

The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of BENLYSTA is not recommended in these situations.

### **2 DOSAGE AND ADMINISTRATION**

#### **2.1 Dosage Schedule**

BENLYSTA is for intravenous infusion **only** and must be reconstituted and diluted prior to administration [see *Dosage and Administration* 2.3)]. Do not administer as an intravenous push or bolus.

The recommended dosage regimen is 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Reconstitute, dilute and administer as an intravenous infusion only, over a period of 1 hour. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a serious hypersensitivity reaction [see *Contraindications* (4), *Warnings and Precautions* (5.4)].

#### **2.2 Premedication Recommendations**

Prior to dosing with BENLYSTA, consider administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions. [see *Warnings and Precautions* (5.4, 5.5) and *Adverse Reactions* (6.1)].

#### **2.3 Preparation of Solutions**

BENLYSTA is provided as a lyophilized powder in a single-use vial for intravenous infusion only and should be reconstituted and diluted by a healthcare professional using aseptic technique as follows:

##### **Reconstitution Instructions**

1. Remove BENLYSTA from the refrigerator and allow to stand 10 to 15 minutes for the vial to reach room temperature.
2. Reconstitute the BENLYSTA powder with Sterile Water for Injection, USP, as follows. The reconstituted solution will contain a concentration of 80 mg/mL belimumab.
  - Reconstitute the 120 mg vial with 1.5 mL Sterile Water for Injection, USP.
  - Reconstitute the 400 mg vial with 4.8 mL Sterile Water for Injection, USP.
3. The stream of sterile water should be directed toward the side of the vial to minimize foaming. Gently swirl the vial for 60 seconds. Allow the vial to sit at room temperature during reconstitution, gently swirling the vial for 60 seconds every 5 minutes until the powder is dissolved. *Do not shake*. Reconstitution is typically complete within 10 to 15 minutes after the sterile water has been added, but it may take up to 30 minutes. Protect

- the reconstituted solution from sunlight.
- If a mechanical reconstitution device (swirler) is used to reconstitute BENLYSTA, it should not exceed 500 rpm and the vial swirled for no longer than 30 minutes.
  - Once reconstitution is complete, the solution should be opalescent and colorless to pale yellow, and without particles. Small air bubbles, however, are expected and acceptable.

#### **Dilution Instructions**

- Dextrose intravenous solutions are incompatible with BENLYSTA. BENLYSTA should only be diluted in 0.9% Sodium Chloride Injection, USP. Dilute the reconstituted product to 250 mL in 0.9% Sodium Chloride Injection, USP (normal saline) for intravenous infusion. From a 250-mL infusion bag or bottle of normal saline, withdraw and discard a volume equal to the volume of the reconstituted solution of BENLYSTA required for the patient's dose. Then add the required volume of the reconstituted solution of BENLYSTA into the infusion bag or bottle. Gently invert the bag or bottle to mix the solution. Any unused solution in the vials must be discarded.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the solution if any particulate matter or discoloration is observed.
- The reconstituted solution of BENLYSTA, if not used immediately, should be stored protected from direct sunlight and refrigerated at 2° to 8°C (36° to 46°F). Solutions of BENLYSTA diluted in normal saline may be stored at 2° to 8°C (36° to 46°F) or room temperature. The total time from reconstitution of BENLYSTA to completion of infusion should not exceed 8 hours.
- No incompatibilities between BENLYSTA and polyvinylchloride or polyolefin bags have been observed.

#### **2.4 Administration Instructions**

- The diluted solution of BENLYSTA should be administered by intravenous infusion only, over a period of 1 hour.
- BENLYSTA should be administered by healthcare providers prepared to manage anaphylaxis. [see *Warnings and Precautions* (5.4)]
- BENLYSTA should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of BENLYSTA with other agents.

### **3 DOSAGE FORMS AND STRENGTHS**

Single-use vials of belimumab lyophilized powder for injection:

- 120 mg per vial
- 400 mg per vial

### **4 CONTRAINDICATIONS**

BENLYSTA is contraindicated in patients who have had anaphylaxis with belimumab.

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Mortality**

There were more deaths reported with BENLYSTA than with placebo during the controlled period of the clinical trials. Out of 2133 patients in 3 clinical trials, a total of 14 deaths occurred

during the placebo-controlled, double-blind treatment periods: 3/675 (0.4%), 5/673 (0.7%), 0/111 (0%), and 6/674 (0.9%) deaths in the placebo, BENLYSTA 1 mg/kg, BENLYSTA 4 mg/kg, and BENLYSTA 10 mg/kg groups, respectively. No single cause of death predominated. Etiologies included infection, cardiovascular disease and suicide.

## 5.2 Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including BENLYSTA. Physicians should exercise caution when considering the use of BENLYSTA in patients with chronic infections. Patients receiving any therapy for chronic infection should not begin therapy with BENLYSTA. Consider interrupting BENLYSTA therapy in patients who develop a new infection while undergoing treatment with BENLYSTA and monitor these patients closely.

In the controlled clinical trials, the overall incidence of infections was 71% in patients treated with BENLYSTA compared with 67% in patients who received placebo. The most frequent infections (>5% of patients receiving BENLYSTA) were upper respiratory tract infection, urinary tract infection, nasopharyngitis, sinusitis, bronchitis, and influenza. Serious infections occurred in 6.0% of patients treated with BENLYSTA and in 5.2% of patients who received placebo. The most frequent serious infections included pneumonia, urinary tract infection, cellulitis, and bronchitis. Infections leading to discontinuation of treatment occurred in 0.7% of patients receiving BENLYSTA and 1.0% of patients receiving placebo. Infections resulting in death occurred in 0.3% (4/1458) of patients treated with BENLYSTA and in 0.1% (1/675) of patients receiving placebo.

## 5.3 Malignancy

The impact of treatment with BENLYSTA on the development of malignancies is not known. In the controlled clinical trials, malignancies (including non-melanoma skin cancers) were reported in 0.4% of patients receiving BENLYSTA and 0.4% of patients receiving placebo. In the controlled clinical trials, malignancies, excluding non-melanoma skin cancers, were observed in 0.2% (3/1458) and 0.3% (2/675) of patients receiving BENLYSTA and placebo, respectively. As with other immunomodulating agents, the mechanism of action of BENLYSTA could increase the risk for the development of malignancies.

## 5.4 Hypersensitivity Reactions, Including Anaphylaxis

In the controlled clinical trials, hypersensitivity reactions (occurring on the same day of infusion) were reported in 13% (191/1458) of patients receiving BENLYSTA and 11% (76/675) of patients receiving placebo. Anaphylaxis was observed in 0.6% (9/1458) of patients receiving BENLYSTA and 0.4% (3/675) of patients receiving placebo. Manifestations included hypotension, angioedema, urticaria or other rash, pruritus, and dyspnea. Due to overlap in signs and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases [see Warnings and Precautions (5.5)]. Some patients (13%) received premedication, which may have mitigated or masked a hypersensitivity response; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of hypersensitivity reactions.

BENLYSTA should be administered by healthcare providers prepared to manage anaphylaxis. In the event of a serious reaction, administration of BENLYSTA must be discontinued immediately and appropriate medical therapy administered. Patients should be monitored during and for an appropriate period of time after administration of BENLYSTA. Patients should be informed of the signs and symptoms of a hypersensitivity reaction and instructed to seek immediate medical care should a reaction occur.

## 5.5 Infusion Reactions

In the controlled clinical trials, adverse events associated with the infusion (occurring on the same day of the infusion) were reported in 17% (251/1458) of patients receiving BENLYSTA and 15% (99/675) of patients receiving placebo. Serious infusion reactions (excluding hypersensitivity reactions) were reported in 0.5% of patients receiving BENLYSTA and 0.4% of patients receiving placebo and included bradycardia, myalgia, headache, rash, urticaria, and hypotension. The most common infusion reactions ( $\geq 3\%$  of patients receiving BENLYSTA) were headache, nausea, and skin reactions. Due to overlap in signs and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases [see *Warnings and Precautions* (5.4)]. Some patients (13%) received premedication, which may have mitigated or masked an infusion reaction; however there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion reactions [see *Adverse Reactions* (6.1)].

BENLYSTA should be administered by healthcare providers prepared to manage infusion reactions. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. Healthcare providers should be aware of the risk of hypersensitivity reactions, which may present as infusion reactions, and monitor patients closely.

## 5.6 Depression

In the controlled clinical trials, psychiatric events were reported more frequently with BENLYSTA (16%) than with placebo (12%), related primarily to depression-related events (6.3% BENLYSTA and 4.7% placebo), insomnia (6.0% BENLYSTA and 5.3% placebo), and anxiety (3.9% BENLYSTA and 2.8% placebo). Serious psychiatric events were reported in 0.8% of patients receiving BENLYSTA (0.6% and 1.2% with 1 and 10 mg/kg, respectively) and 0.4% of patients receiving placebo. Serious depression was reported in 0.4% (6/1458) of patients receiving BENLYSTA and 0.1% (1/675) of patients receiving placebo. Two suicides (0.1%) were reported in patients receiving BENLYSTA. The majority of patients who reported serious depression or suicidal behavior had a history of depression or other serious psychiatric disorders and most were receiving psychoactive medications. It is unknown if BENLYSTA treatment is associated with increased risk for these events.

Patients receiving BENLYSTA should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts, or other mood changes.

## 5.7 Immunization

Live vaccines should not be given for 30 days before or concurrently with BENLYSTA as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving BENLYSTA or the effect of

BENLYSTA on new immunizations. Because of its mechanism of action, BENLYSTA may interfere with the response to immunizations.

### **5.8 Concomitant Use with Other Biologic Therapies or Intravenous Cyclophosphamide**

BENLYSTA has not been studied in combination with other biologic therapies, including B-cell targeted therapies, or intravenous cyclophosphamide. Therefore, use of BENLYSTA is not recommended in combination with biologic therapies or intravenous cyclophosphamide.

## **6 ADVERSE REACTIONS**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following have been observed with BENLYSTA and are discussed in detail in the Warnings and Precautions section:

- **Mortality** [see Warnings and Precautions (5.1)]
- **Serious Infections** [see Warnings and Precautions (5.2)]
- **Malignancy** [see Warnings and Precautions (5.3)]
- **Hypersensitivity Reactions, Including Anaphylaxis** [see Warnings and Precautions (5.4)]
- **Infusion reactions** [see Warnings and Precautions (5.5)]
- **Depression** [see Warnings and Precautions (5.6)]

### **6.1 Clinical Trials Experience**

The data described below reflect exposure to BENLYSTA plus standard of care compared with placebo plus standard of care in 2133 patients in 3 controlled studies. Patients received BENLYSTA at doses of 1 mg/kg (N=673), 4 mg/kg (N=111; Trial 1 only), or 10 mg/kg (N=674) or placebo (N=675) intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days. In two of the studies (Trial 1 and Trial 3), treatment was given for 48 weeks, while in the other study (Trial 2) treatment was given for 72 weeks [see Clinical Studies (14)]. Because there was no apparent dose-related increase in the majority of adverse events observed with BENLYSTA, the safety data summarized below are presented for the 3 doses pooled, unless otherwise indicated; the adverse reaction table displays the results for the recommended dose of 10 mg/kg compared with placebo.

The population had a mean age of 39 (range 18-75), 94% were female, and 52% were Caucasian. In these trials, 93% of patients treated with BENLYSTA reported an adverse reaction compared with 92% treated with placebo.

The most common serious adverse reactions were serious infections (6.0% and 5.2% in the groups receiving BENLYSTA and placebo, respectively) [see Warnings and Precautions (5.2)].

The most commonly-reported adverse reactions, occurring in ≥5% of patients in clinical trials were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis.

The proportion of patients who discontinued treatment due to any adverse reaction during the controlled clinical trials was 6.2% for patients receiving BENLYSTA and 7.1% for patients receiving placebo. The most common adverse reactions resulting in discontinuation of treatment ( $\geq 1\%$  of patients receiving BENLYSTA or placebo) were infusion reactions (1.6% BENLYSTA and 0.9% placebo), lupus nephritis (0.7% BENLYSTA and 1.2% placebo), and infections (0.7% BENLYSTA and 1.0% placebo).

Table 1 lists adverse reactions, regardless of causality, occurring in at least 3% of patients with SLE who received BENLYSTA 10 mg/kg and at an incidence at least 1% greater than that observed with placebo in the 3 controlled studies.

**Table 1 Incidence of Adverse Reactions Occurring in at Least 3% of Patients Treated With BENLYSTA 10 mg/kg Plus Standard of Care and at Least 1% More Frequently Than in Patients Receiving Placebo plus Standard of Care in 3 Controlled SLE Studies**

Preferred Term	BENLYSTA 10 mg/kg + Standard of Care (n = 674) %	Placebo + Standard of Care (n = 675) %
Nausea	15	12
Diarrhea	12	9
Pyrexia	10	8
Nasopharyngitis	9	7
Bronchitis	9	5
Insomnia	7	5
Pain in extremity	6	4
Depression	5	4
Migraine	5	4
Pharyngitis	5	3
Cystitis	4	3
Leukopenia	4	2
Gastroenteritis viral	3	1

## 6.2 Immunogenicity

In Trials 2 and 3, anti-belimumab antibodies were detected in 4 of 563 (0.7%) patients receiving BENLYSTA 10 mg/kg and in 27 of 559 (4.8%) patients receiving BENLYSTA 1 mg/kg. The reported frequency for the group receiving 10 mg/kg may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentrations. Neutralizing antibodies were detected in 3 patients receiving BENLYSTA 1 mg/kg. Three patients with anti-belimumab antibodies experienced mild infusion reactions of nausea, erythematous rash, pruritus, eyelid edema, headache, and dyspnea; none of the reactions was life-threatening. The clinical relevance of the presence of anti-belimumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to belimumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology,



sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to belimumab with the incidence of antibodies to other products may be misleading.

## **7 DRUG INTERACTIONS**

Formal drug interaction studies have not been performed with BENLYSTA. In clinical trials of patients with SLE, BENLYSTA was administered concomitantly with other drugs, including corticosteroids, antimalarials, immunomodulatory and immunosuppressive agents (including azathioprine, methotrexate, and mycophenolate), angiotensin pathway antihypertensives, HMG-CoA reductase inhibitors (statins), and NSAIDs without evidence of a clinically meaningful effect of these concomitant medications on belimumab pharmacokinetics. The effect of belimumab on the pharmacokinetics of other drugs has not been evaluated [see *Pharmacokinetics 12.3*].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C. There are no adequate and well-controlled clinical studies using BENLYSTA in pregnant women. Immunoglobulin G (IgG) antibodies, including BENLYSTA, can cross the placenta. Because animal reproduction studies are not always predictive of human response, BENLYSTA should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Women of childbearing potential should use adequate contraception during treatment with BENLYSTA and for at least 4 months after the final treatment.

Nonclinical reproductive studies have been performed in pregnant cynomolgus monkeys receiving belimumab at doses of 0, 5 and 150 mg/kg by intravenous infusion (the high dose was approximately 9 times the anticipated maximum human exposure) every 2 weeks from gestation day 20 to 150. Belimumab was shown to cross the placenta. Belimumab was not associated with direct or indirect teratogenicity under the conditions tested. Fetal deaths were observed in 14%, 24% and 15% of pregnant females in the 0, 5 and 150 mg/kg groups, respectively. Infant deaths occurred with an incidence of 0%, 8% and 5%. The cause of fetal and infant deaths is not known. The relevance of these findings to humans is not known. Other treatment-related findings were limited to the expected reversible reduction of B cells in both dams and infants and reversible reduction of IgM in infant monkeys. B-cell numbers recovered after the cessation of belimumab treatment by about 1 year post-partum in adult monkeys and by 3 months of age in infant monkeys. IgM levels in infants exposed to belimumab in utero recovered by 6 months of age.

**Pregnancy Registry:** To monitor maternal-fetal outcomes of pregnant women exposed to BENLYSTA, a pregnancy registry has been established. Healthcare professionals are encouraged to register patients and pregnant women are encouraged to enroll themselves by calling 1-877-681-6296.

### **8.3 Nursing Mothers**

It is not known whether BENLYSTA is excreted in human milk or absorbed systemically after ingestion. However, belimumab was excreted into the milk of cynomolgus monkeys. Because

maternal antibodies are excreted in human breast milk, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of breastfeeding to the infant and the importance of the drug to the mother.

#### **8.4 Pediatric Use**

Safety and effectiveness of BENLYSTA have not been established in children.

#### **8.5 Geriatric Use**

Clinical studies of BENLYSTA did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects. Use with caution in elderly patients.

#### **8.6 Race**

In Trial 2 and Trial 3, response rates for the primary endpoint were lower for black subjects in the BENLYSTA group relative to black subjects in the placebo group [see *Clinical Studies (14)*]. Use with caution in black/African-American patients.

### **10 OVERDOSAGE**

There is no clinical experience with overdosage of BENLYSTA. Two doses of up to 20 mg/kg have been given by intravenous infusion to humans with no increase in incidence or severity of adverse reactions compared with doses of 1, 4, or 10 mg/kg.

### **11 DESCRIPTION**

BENLYSTA (belimumab) is a human IgG1 $\lambda$  monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab has a molecular weight of approximately 147 kDa. Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

BENLYSTA is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for intravenous infusion. Upon reconstitution with Sterile Water for Injection, USP, [see *Dosage and Administration (2.3)*] each single-use vial delivers 80 mg/mL belimumab in 0.16 mg/mL citric acid, 0.4 mg/mL polysorbate 80, 2.7 mg/mL sodium citrate, and 80 mg/mL sucrose, with a pH of 6.5.

### **12 CLINICAL PHARMACOLOGY**

#### **12.1 Mechanism of Action**

BENLYSTA is a BLyS-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells. BENLYSTA does not bind B cells directly, but by binding BLyS, BENLYSTA inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

#### **12.2 Pharmacodynamics**

In Trial 1 and Trial 2 in which B cells were measured, treatment with BENLYSTA significantly reduced circulating CD19+, CD20+, naïve, and activated B cells, plasmacytoid cells, and the SLE B-cell subset at Week 52. Reductions in naïve and the SLE B-cell subset were observed as early as Week 8 and were sustained to Week 52. Memory cells increased initially and slowly

declined toward baseline levels by Week 52. The clinical relevance of these effects on B cells has not been established.

Treatment with BENLYSTA led to reductions in IgG and anti-dsDNA, and increases in complement (C3 and C4). These changes were observed as early as Week 8 and were sustained through Week 52. The clinical relevance of normalizing these biomarkers has not been definitively established.

### 12.3 Pharmacokinetics

The pharmacokinetic parameters displayed in Table 2 are based on population parameter estimates which are specific to the 563 patients who received belimumab 10 mg/kg in Trials 2 and 3 [see *Clinical Studies* (14)].

**Table 2. Population Pharmacokinetic Parameters in Patients with SLE after Intravenous Infusion of BENLYSTA 10 mg/kg<sup>1</sup>**

Pharmacokinetic Parameter	Population Estimates (n = 563)
Peak concentration ( $C_{max}$ , $\mu\text{g/mL}$ )	313
Area under the curve ( $AUC_{0-\infty}$ , $\text{day} \cdot \mu\text{g/mL}$ )	3,083
Distribution half-life ( $t_{1/2}$ , days)	1.75
Terminal half-life ( $t_{1/2}$ , days)	19.4
Systemic clearance (CL, $\text{mL/day}$ )	215
Volume of distribution ( $V_{ss}$ , L)	5.29

<sup>1</sup> Intravenous infusions were administered at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

**Drug Interactions:** No formal drug interaction studies have been conducted with belimumab. Concomitant use of mycophenolate, azathioprine, methotrexate, antimalarials, NSAIDs, aspirin, and HMG-CoA reductase inhibitors did not significantly influence belimumab pharmacokinetics. Coadministration of steroids and angiotensin-converting enzyme (ACE) inhibitors resulted in an increase of systemic clearance of belimumab that was not clinically significant because the magnitude was well within the range of normal variability of clearance. The effect of belimumab on the pharmacokinetics of other drugs has not been evaluated.

#### Special Populations:

The following information is based on the population pharmacokinetic analysis.

**Age:** Age did not significantly influence belimumab pharmacokinetics in the study population, where the majority of subjects (70%) were between 18 and 45 years of age. No pharmacokinetic data are available in pediatric patients. Limited pharmacokinetic data are available for elderly patients as only 1.4% of the subjects included in the pharmacokinetic analysis were 65 years of age or older [see *Use in Specific Populations* (8.5)].

**Gender:** Gender did not significantly influence belimumab pharmacokinetics in the largely (94%) female study population.

**Race:** Race did not significantly influence belimumab pharmacokinetics. The racial distribution was 53% white/Caucasian, 16% Asian, 16% Alaska native/American Indian, and 14% black/African American.

**Renal Impairment:** No formal studies were conducted to examine the effects of renal impairment on the pharmacokinetics of belimumab. Belimumab has been studied in a limited number of patients with SLE and renal impairment (261 subjects with moderate renal impairment, creatinine clearance  $\geq 30$  and  $< 60$  mL/min; 14 subjects with severe renal impairment, creatinine clearance  $\geq 15$  and  $< 30$  mL/min). Although increases in creatinine clearance and proteinuria ( $> 2$  g/day) increased belimumab clearance, these effects were within the expected range of variability. Therefore, dosage adjustment in patients with renal impairment is not recommended.

**Hepatic Impairment:** No formal studies were conducted to examine the effects of hepatic impairment on the pharmacokinetics of belimumab. Belimumab has not been studied in patients with severe hepatic impairment. Baseline ALT and AST levels did not significantly influence belimumab pharmacokinetics.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term animal studies have not been performed to evaluate the carcinogenic potential of belimumab. The mutagenic potential of belimumab was not evaluated.

Effects on male and female fertility have not been directly evaluated in animal studies.

## **14 CLINICAL STUDIES**

The safety and effectiveness of BENLYSTA were evaluated in three randomized, double-blind, placebo-controlled studies involving 2133 patients with SLE according to the American College of Rheumatology criteria (Trial 1, 2, and 3). Patients with severe active lupus nephritis and severe active CNS lupus were excluded. Patients were on a stable standard of care SLE treatment regimen comprising any of the following (alone or in combination): corticosteroids, antimalarials, NSAIDs, and immunosuppressives. Use of other biologics and intravenous cyclophosphamide were not permitted.

### **Trial 1: BENLYSTA 1 mg/kg, 4 mg/kg, 10 mg/kg**

Trial 1 enrolled 449 patients and evaluated doses of 1, 4, and 10 mg/kg BENLYSTA plus standard of care compared with placebo plus standard of care over 52 weeks in patients with SLE. Patients had to have a SELENA-SLEDAI score of  $\geq 4$  at baseline and a history of autoantibodies (anti-nuclear antibody (ANA) and/or anti-double-stranded DNA (anti-dsDNA)), but 28% of the population was autoantibody negative at baseline. The co-primary endpoints were percent change in SELENA-SLEDAI score at Week 24 and time to first flare over 52 weeks. No significant differences between any of the BENLYSTA groups and the placebo group were observed. Exploratory analysis of this study identified a subgroup of patients (72%), who were autoantibody positive, in whom BENLYSTA appeared to offer benefit. The results of

this study informed the design of Trials 2 and 3 and led to the selection of a target population and indication that is limited to autoantibody-positive SLE patients.

***Trials 2 and 3: BENLYSTA 1 mg/kg and 10 mg/kg***

Trials 2 and 3 were randomized, double-blind, placebo-controlled trials in patients with SLE that were similar in design except duration - Trial 2 was 76 weeks duration and Trial 3 was 52 weeks duration. Eligible patients had active SLE disease, defined as a SELENA-SLEDAI score  $\geq 6$ , and positive autoantibody test results at screening. Patients were excluded from the study if they had ever received treatment with a B-cell targeted agent or if they were currently receiving other biologic agents. Intravenous cyclophosphamide was not permitted within the previous 6 months or during study. Trial 2 was conducted primarily in North America and Europe. Trial 3 was conducted in South America, Eastern Europe, Asia, and Australia.

Baseline concomitant medications included corticosteroids (Trial 2: 76%, Trial 3: 96%), immunosuppressives (Trial 2: 56%, Trial 3: 42%; including azathioprine, methotrexate and mycophenolate), and antimalarials (Trial 2: 63%, Trial 3: 67%). Most patients (>70%) were receiving 2 or more classes of SLE medications.

In Trial 2 and Trial 3, more than 50% of patients had 3 or more active organ systems at baseline. The most common active organ systems at baseline based on SELENA SLEDAI were mucocutaneous (82% in both studies); immunology (Trial 2: 74%, Trial 3: 85%); and musculoskeletal (Trial 2: 73%, Trial 3: 59%). Less than 16% of patients had some degree of renal activity and less than 7% of patients had activity in the vascular, cardio-respiratory, or CNS systems.

At screening, patients were stratified by disease severity based on their SELENA-SLEDAI score ( $\leq 9$  vs  $\geq 10$ ), proteinuria level ( $< 2$  g/24 hr vs  $\geq 2$  g/24 hr), and race (African or Indigenous-American descent vs. other), and then randomly assigned to receive BENLYSTA 1 mg/kg, BENLYSTA 10 mg/kg, or placebo in addition to standard of care. The patients were administered study medication intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days for 48 weeks in Trial 3 and for 72 weeks in Trial 2.

The primary efficacy endpoint was a composite endpoint (SLE Responder Index or SRI) that defined response as meeting each of the following criteria at Week 52 compared with baseline:

- $\geq 4$ -point reduction in the SELENA-SLEDAI score, and
- no new British Isles Lupus Assessment Group (BILAG) A organ domain score or 2 new BILAG B organ domain scores, and
- no worsening ( $< 0.30$ -point increase) in Physician's Global Assessment (PGA) score.

The SRI uses the SELENA-SLEDAI score as an objective measure of reduction in global disease activity; the BILAG index to ensure no significant worsening in any specific organ system; and the PGA to ensure that improvements in disease activity are not accompanied by worsening of the patient's condition overall.

In both Trials 2 and 3, the proportion of SLE patients achieving an SRI response, as defined for the primary endpoint, was significantly higher in the BENLYSTA 10 mg/kg group than in the

placebo group in both studies. The effect on the SRI was not consistently significantly different for the BENLYSTA 1 mg/kg group relative to placebo in both trials. The 1 mg/kg dose is not recommended. The trends in comparisons between the treatment groups for the rates of response for the individual components of the endpoint were generally consistent with that of the SRI (Table 3). At Week 76 in Trial 2, the SRI response rate with BENLYSTA 10 mg/kg was not significantly different from that of placebo (39% and 32%, respectively).

**Table 3. Clinical Response Rate in Patients with SLE After 52 Weeks of Treatment**

Response <sup>1</sup>	Trial 2			Trial 3		
	Placebo + Standard of Care (n = 275)	BENLYSTA 1 mg/kg + Standard of Care <sup>2</sup> (n = 271)	BENLYSTA 10 mg/kg + Standard of Care (n = 273)	Placebo + Standard of Care (n = 287)	BENLYSTA 1 mg/kg + Standard of Care <sup>2</sup> (n = 288)	BENLYSTA 10 mg/kg + Standard of Care (n = 290)
SLE Responder Index	34%	41%	43%	44%	51%	58%
		(p = 0.104)	(p = 0.021)		(p = 0.013)	(p < 0.001)
Odds Ratio (95% CI) vs. placebo		1.3 (0.9, 1.9)	1.5 (1.1, 2.2)		1.6 (1.1, 2.2)	1.8 (1.3, 2.6)
Components of SLE Responder Index						
Percent of patients with reduction in SELENA-SLEDAI ≥4	36%	43%	47%	46%	53%	58%
Percent of patients with no worsening by BILAG index	65%	75%	69%	73%	79%	81%
Percent of patients with no worsening by PGA	63%	73%	69%	69%	79%	80%

<sup>1</sup>Patients dropping out of the study early or experiencing certain increases in background medication were considered as failures in these analyses. In both studies, a higher proportion of placebo patients were considered as failures for this reason as compared to the BENLYSTA groups.

<sup>2</sup>The 1 mg/kg dose is not recommended.

The reduction in disease activity seen in the SRI was related primarily to improvement in the most commonly involved organ systems namely, mucocutaneous, musculoskeletal, and immunology.

#### *Effect in Black/African-American Patients*

Exploratory sub-group analyses of SRI response rate in patients of black race were performed. In Trial 2 and Trial 3 combined, the SRI response rate in black patients (N=148) in the BENLYSTA groups was less than that in the placebo group (22/50 or 44% for placebo, 15/48 or 31% for BENLYSTA 1 mg/kg, and 18/50 or 36% for BENLYSTA 10 mg/kg). In Trial 1, black patients (N=106) in the BENLYSTA groups did not appear to have a different response than the

rest of the study population. Although no definitive conclusions can be drawn from these subgroup analyses, caution should be used when considering BENLYSTA treatment in black/African-American SLE patients.

#### *Effect on Concomitant Steroid Treatment:*

In Trial 2 and Trial 3, 46% and 69% of patients, respectively, were receiving prednisone at doses > 7.5 mg/day at baseline. The proportion of patients able to reduce their average prednisone dose by at least 25% to ≤7.5 mg/day during Weeks 40 through 52 was not consistently significantly different for BENLYSTA relative to placebo in both trials. In Trial 2, 17% of patients receiving BENLYSTA 10 mg/kg and 19% of patients receiving BENLYSTA 1 mg/kg achieved this level of steroid reduction compared with 13% of patients receiving placebo. In Trial 3, 19%, 21%, and 12% of patients receiving BENLYSTA 10 mg/kg, BENLYSTA 1 mg/kg, and placebo, respectively, achieved this level of steroid reduction.

#### *Effect on Severe SLE Flares:*

The probability of experiencing a severe SLE flare, as defined by a modification of the SELENA Trial flare criteria which excluded severe flares triggered only by an increase of the SELENA-SLEDAI score to >12, was calculated for both Trials 2 and 3. The proportion of patients having at least 1 severe flare over 52 weeks was not consistently significantly different for BENLYSTA relative to placebo in both trials. In Trial 2, 18% of patients receiving BENLYSTA 10 mg/kg and 16% of patients receiving BENLYSTA 1 mg/kg had a severe flare compared with 24% of patients receiving placebo. In Trial 3, 14%, 18%, and 23% of patients receiving BENLYSTA 10 mg/kg, BENLYSTA 1 mg/kg and placebo, respectively, had a severe flare.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

BENLYSTA is a sterile, preservative-free lyophilized powder for reconstitution, dilution, and intravenous infusion provided in single-use glass vials with a latex-free rubber stopper and a flip-off seal. Each 5-mL vial contains 120 mg of belimumab. Each 20-mL vial contains 400 mg of belimumab.

BENLYSTA is supplied as follows:

120 mg belimumab in a 5-mL single-use vial	NDC 49401-101-01
400 mg belimumab in a 20-mL single-use vial	NDC 49401-102-01

Store vials of BENLYSTA refrigerated between 2° to 8°C (36° to 46°F). Vials should be protected from light and stored in the original carton until use. *Do not freeze.* Avoid exposure to heat. Do not use beyond the expiration date.

## **17 PATIENT COUNSELING INFORMATION**

*See Medication Guide.*

### **17.1 Advice for the Patient**

Patients should be given the Medication Guide for BENLYSTA and provided an opportunity to read it prior to each treatment session. It is important that the patient's overall health be assessed at each infusion visit and any questions resulting from the patient's reading of the Medication Guide be discussed.

**Mortality:** Patients should be advised that more patients receiving BENLYSTA in the main clinical trials died than did patients receiving placebo treatment [see *Warnings and Precautions* (5.1)].

**Serious Infections:** Patients should be advised that BENLYSTA may decrease their ability to fight infections. Patients should be asked if they have a history of chronic infections and if they are currently on any therapy for an infection [see *Warnings and Precautions* (5.2)]. Patients should be instructed to tell their healthcare provider if they develop signs or symptoms of an infection.

**Hypersensitivity/Anaphylactic and Infusion Reactions:** Educate patients on the signs and symptoms of anaphylaxis, including wheezing, difficulty breathing, peri-oral or lingual edema, and rash. Patients should be instructed to immediately tell their healthcare provider if they experience symptoms of an allergic reaction during or after the administration of BENLYSTA [see *Warnings and Precautions* (5.4, 5.5)].

**Depression:** Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or other mood changes. [see *Warnings and Precautions* (5.6)].

**Immunizations:** Patients should be informed that they should not receive live vaccines while taking BENLYSTA. Response to vaccinations could be impaired by BENLYSTA [see *Warnings and Precautions* (5.7)].

**Pregnancy and Nursing Mothers:** Patients should be informed that BENLYSTA has not been studied in pregnant women or nursing mothers so the effects of BENLYSTA on pregnant women or nursing infants are not known. Patients should be instructed to tell their healthcare provider if they are pregnant, become pregnant, or are thinking about becoming pregnant [see *Use in Specific Populations* (8.1)]. Patients should be instructed to tell their healthcare provider if they plan to breastfeed their infant [see *Use in Specific Populations* (8.3)].



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Rockville, Maryland 20850  
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Human Genome Sciences, Inc.  
Rockville, MD 20850



GlaxoSmithKline  
Research Triangle Park, NC 27709

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## MEDICATION GUIDE

### **BENLYSTA<sup>®</sup>** (ben-LIST-ah) (belimumab)

#### **Injection for intravenous use**

Read this Medication Guide before you start receiving BENLYSTA and before each treatment. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

#### **What is the most important information I should know about BENLYSTA?**

BENLYSTA can cause serious side effects. Some of these side effects may cause death. It is not known if BENLYSTA causes these serious side effects. Tell your healthcare provider right away if you have any of the symptoms listed below while receiving BENLYSTA.

#### **1. Infections.** Symptoms of an infection can include:

- fever
- chills
- pain or burning with urination
- urinating often
- bloody diarrhea
- coughing up mucus

#### **2. Heart Problems.** Symptoms of heart problems can include:

- chest discomfort or pain
- shortness of breath
- cold sweats
- nausea
- dizziness
- discomfort in other areas of the upper body

#### **3. Mental health problems and suicide.** Symptoms of mental health problems can include:

- thoughts of suicide or dying
- attempt to commit suicide
- trouble sleeping (insomnia)
- new or worse anxiety
- new or worse depression
- acting on dangerous impulses
- other unusual changes in your behavior or mood
- thoughts of hurting yourself or others

## **What is BENLYSTA?**

BENLYSTA is a prescription medicine used to treat adults with active systemic lupus erythematosus (SLE or lupus) who are receiving other lupus medicines.

BENLYSTA contains *belimumab* which is in a group of medicines called *monoclonal antibodies*. Lupus is a disease of the immune system (the body system that fights infection). People with active lupus often have high levels of a certain protein in their blood. BENLYSTA binds to and limits the activity of the protein. When given together with other medicines for lupus, BENLYSTA decreases lupus disease activity more than other lupus medicines alone.

- It is not known if BENLYSTA is safe and effective in people with severe active lupus nephritis or severe active central nervous system lupus.
- It is not known if BENLYSTA is safe and effective in children.

## **Who should not receive BENLYSTA?**

### **Do not receive BENLYSTA if you:**

- are allergic to belimumab or any of the ingredients in BENLYSTA. See the end of this Medication Guide for a complete list of ingredients in BENLYSTA.

## **What should I tell my healthcare provider before receiving BENLYSTA?**

Before you receive BENLYSTA, tell your healthcare provider if you:

- think you have an infection or have infections that keep coming back. You should not receive BENLYSTA if you have an infection unless your healthcare provider tells you to. **See “What is the most important information I should know about BENLYSTA.”**
- have or have had mental health problems such as depression or thoughts of suicide
- have recently received a vaccination or if you think you may need a vaccination. If you are receiving BENLYSTA, you should not receive live vaccines.
- are receiving other biologic medicines, monoclonal antibodies or IV infusions of cyclophosphamide (Cytosan<sup>®</sup>)
- have or have had any type of cancer
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if BENLYSTA will harm your unborn baby. Tell your healthcare provider if you become pregnant during your treatment with BENLYSTA.
- If you become pregnant while receiving BENLYSTA, talk to your healthcare provider about enrolling in the BENLYSTA Pregnancy Registry. You can enroll in this registry by calling 1-877-681-6296. The purpose of this registry is to monitor the health of you and your baby.

- are breastfeeding or plan to breastfeed. It is not known if BENLYSTA passes into your breast milk. You and your healthcare provider should decide if you will receive BENLYSTA or breastfeed. You should not do both.

**Tell your healthcare provider about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines with you to show to your healthcare provider and pharmacist when you get a new medicine.

#### **How will I receive BENLYSTA?**

- You will be given BENLYSTA by a healthcare provider through a needle placed in a vein (IV infusion). It takes about 1 hour to give you the full dose of BENLYSTA.
- Your healthcare provider will tell you how often you should receive BENLYSTA.
- Your healthcare provider may give you medicines before you receive BENLYSTA to help reduce your chance of having a reaction. A healthcare provider will watch you closely while you are receiving BENLYSTA and after your infusion for signs of a reaction.

#### **What are the possible side effects of BENLYSTA?**

**BENLYSTA can cause serious side effects.**

- See “What is the most important information I should know about BENLYSTA?”

**1. Cancer.** BENLYSTA may reduce the activity of your immune system. Medicines that affect the immune system may increase your risk of certain cancers.

**2. Allergic (hypersensitivity) and infusion reactions.** Serious allergic or infusion reactions can happen on the day of or the day after receiving BENLYSTA. Symptoms of an allergic or infusion reaction may include:

- itching
- swelling of the face, lips, mouth, tongue, or throat
- trouble breathing
- anxiousness
- low blood pressure
- dizziness or fainting
- headache
- nausea
- skin rash, redness, or swelling

Your healthcare provider will watch you closely while you are receiving BENLYSTA and after your infusion for signs of a reaction.

**The most common side effects of BENLYSTA include:**

- nausea
- diarrhea
- fever
- stuffy or runny nose
- sore throat
- cough (bronchitis)
- trouble sleeping
- leg or arm pain
- headache (migraine)
- urinary tract infection
- decreased white blood cell count (leukopenia)
- vomiting
- stomach pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of BENLYSTA. For more information, ask your healthcare provider.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of BENLYSTA**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BENLYSTA for a condition for which it was not prescribed.

This Medication Guide summarizes the most important information about BENLYSTA. For more information about BENLYSTA, talk with your healthcare provider.

You can ask your healthcare provider or pharmacist for information about BENLYSTA that is written for healthcare professionals.

For more information about BENLYSTA, go to [www.BENLYSTA.com](http://www.BENLYSTA.com) or call 1-877-423-6597.

**What are the ingredients in BENLYSTA?**

**Active ingredient:** belimumab.

**Inactive ingredients:** citric acid, polysorbate 80, sodium citrate, sucrose.

RX Only

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Research Triangle Park, NC 27709

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued: March 2011

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U.S. Patent No. 7,138,501

Application for Patent Term Extension

# **Attachment D**



US007138501B2

**(12) United States Patent**  
**Ruben et al.****(10) Patent No.: US 7,138,501 B2**  
**(45) Date of Patent: Nov. 21, 2006**

- (54) **ANTIBODIES THAT IMMUNOSPECIFICALLY BIND BLYS**
- (75) Inventors: **Steven M. Ruben**, Olney, MD (US);  
**Gil H. Choi**, Rockville, MD (US);  
**Tristan Vaughan**, Great Shelford (GB);  
**David Hilbert**, Bethesda, MD (US)
- (73) Assignee: **Human Genome Sciences, Inc.**,  
Rockville, MD (US)
- (\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 754 days.

(21) Appl. No.: **09/880,748**(22) Filed: **Jun. 15, 2001****(65) Prior Publication Data**

US 2003/0059937 A1 Mar. 27, 2003

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- (60) Provisional application No. 60/293,499, filed on May 25, 2001, provisional application No. 60/277,379, filed on Mar. 21, 2001, provisional application No. 60/276,248, filed on Mar. 16, 2001, provisional application No. 60/240,816, filed on Oct. 17, 2000, provisional application No. 60/212,210, filed on Jun. 16, 2000.
- (51) **Int. Cl.**  
**C07K 16/00** (2006.01)  
**C12P 21/08** (2006.01)
- (52) **U.S. CL.** ..... **530/388.23**; 530/387.1;  
530/387.3; 530/387.9; 530/388.15; 530/391.1;  
530/391.3; 530/391.7
- (58) **Field of Classification Search** ..... 530/387.1,  
530/387.3, 387.9, 388.1, 388.15, 388.23,  
530/389.1, 389.2, 391.1, 391.3, 391.7; 435/326,  
435/328, 331, 335

See application file for complete search history.

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*Primary Examiner*—Patricia A. Duffy  
(74) *Attorney, Agent, or Firm*—Human Genome Sciences, Inc.

**(57) ABSTRACT**

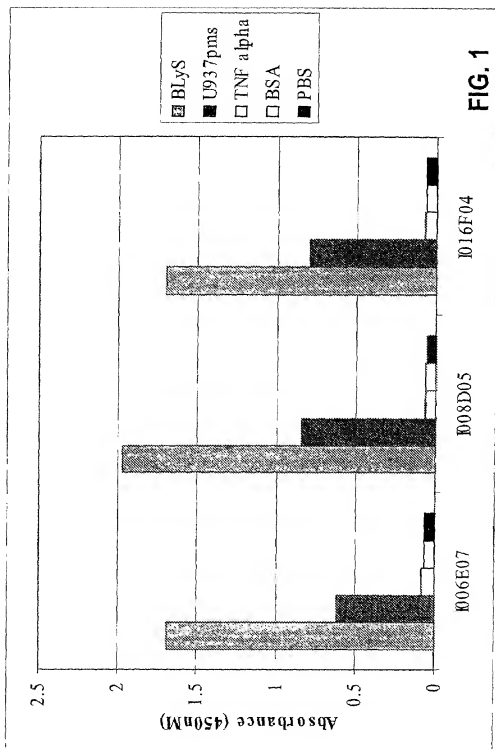
The present invention relates to antibodies and related molecules that immunospecifically bind to B Lymphocyte Stimulator. The present invention also relates to methods and compositions for detecting or diagnosing a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or inappropriate function of B Lymphocyte Stimulator comprising antibodies or fragments or variants thereof or related molecules that immunospecifically bind to B Lymphocyte Stimulator. The present invention further relates to methods and compositions for preventing, treating or ameliorating a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or inappropriate B Lymphocyte Stimulator function comprising administering to an animal an effective amount of one or more antibodies or fragments or variants thereof or related molecules that immunospecifically bind to B Lymphocyte Stimulator.

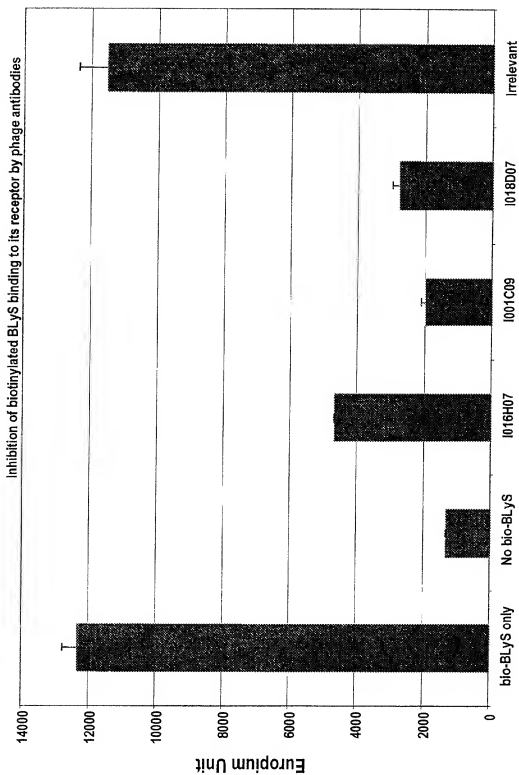


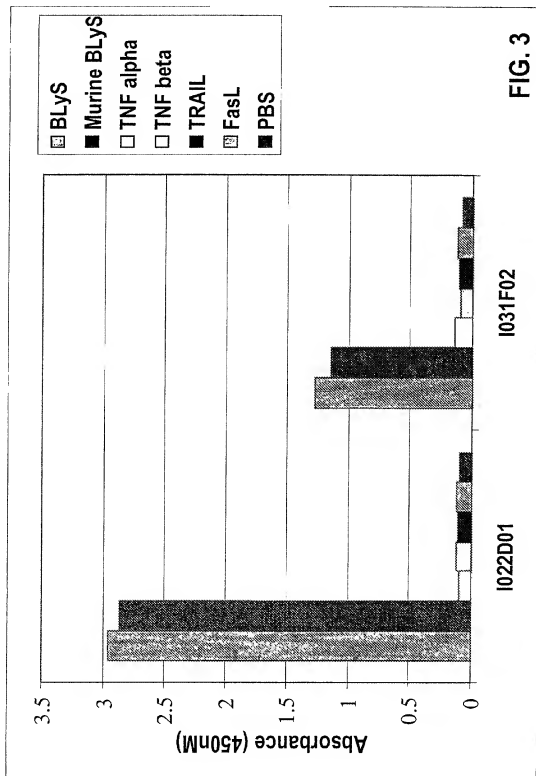
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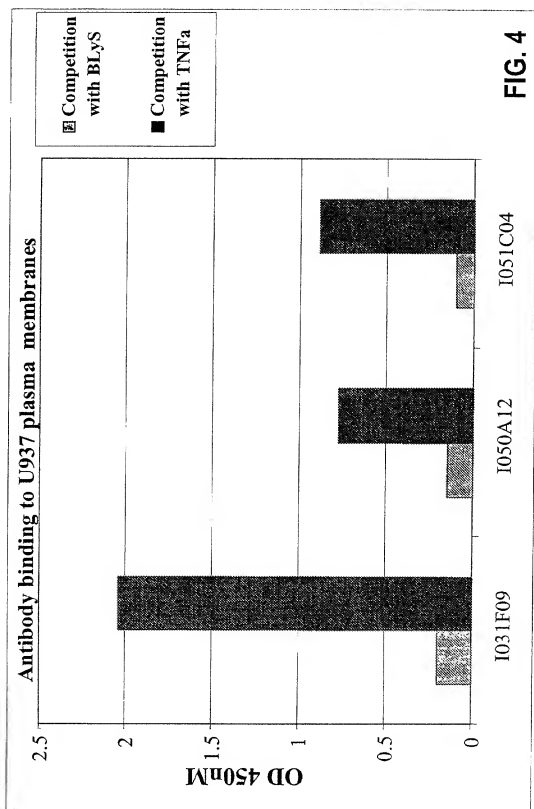
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**FIG. 2**





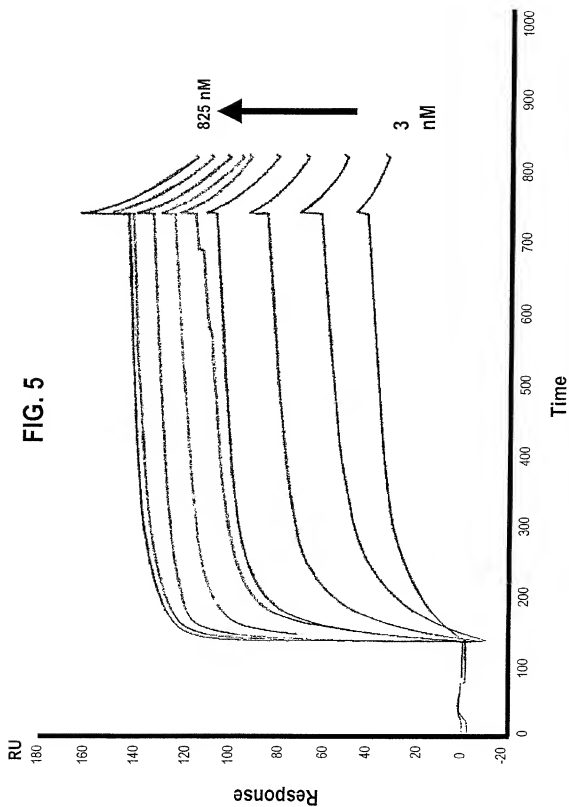
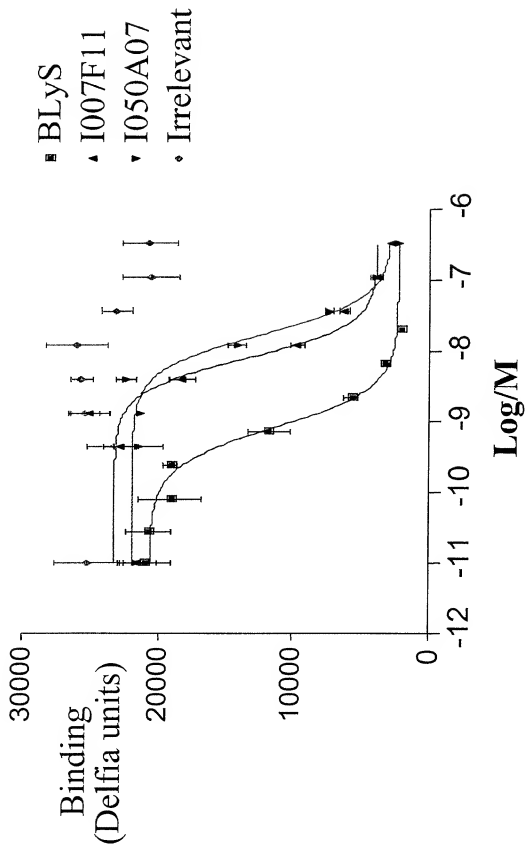


FIG. 6



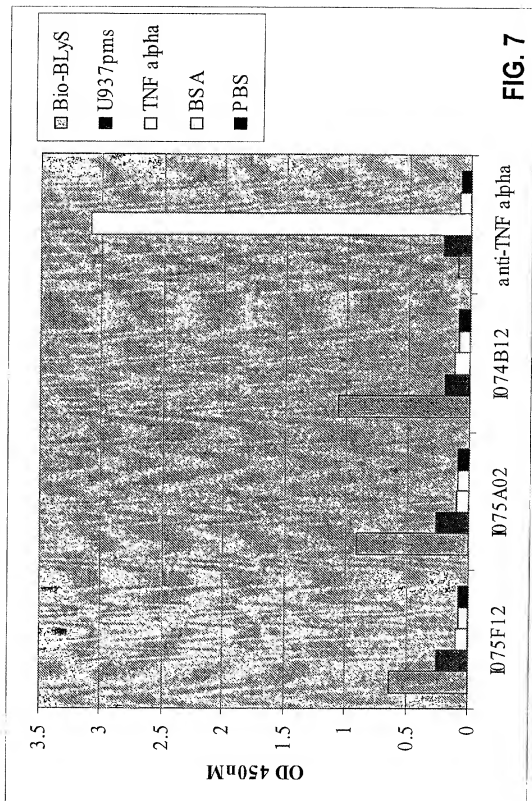
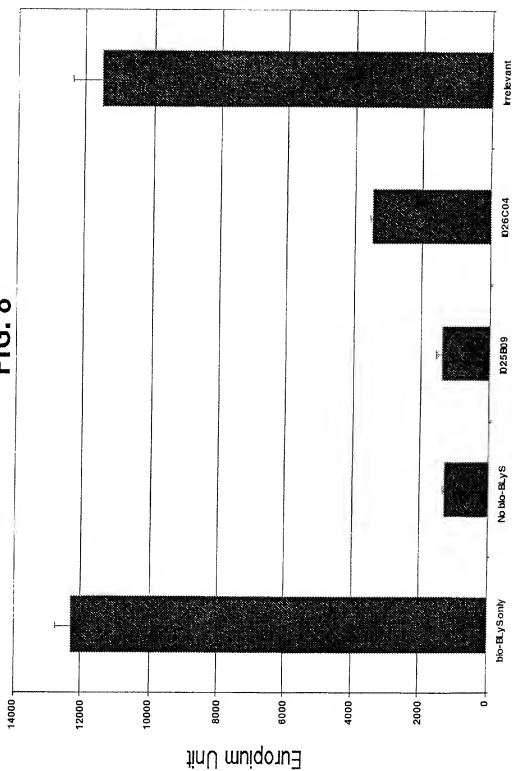
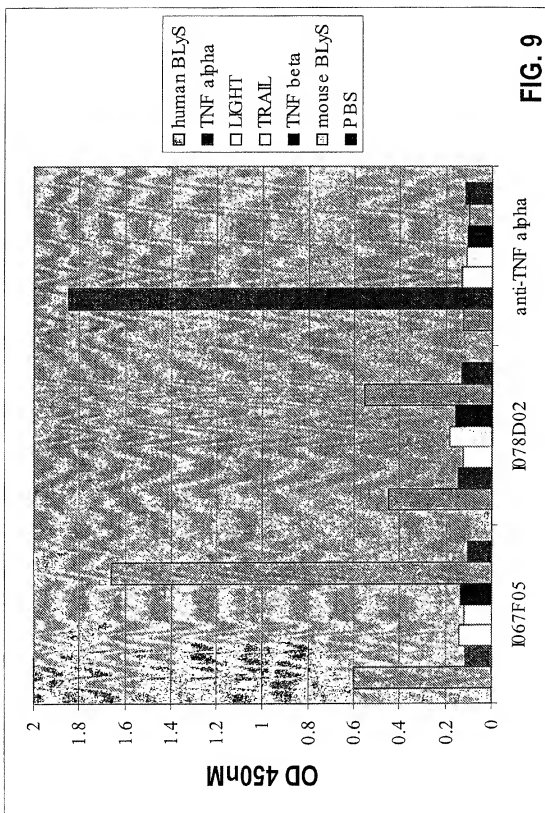
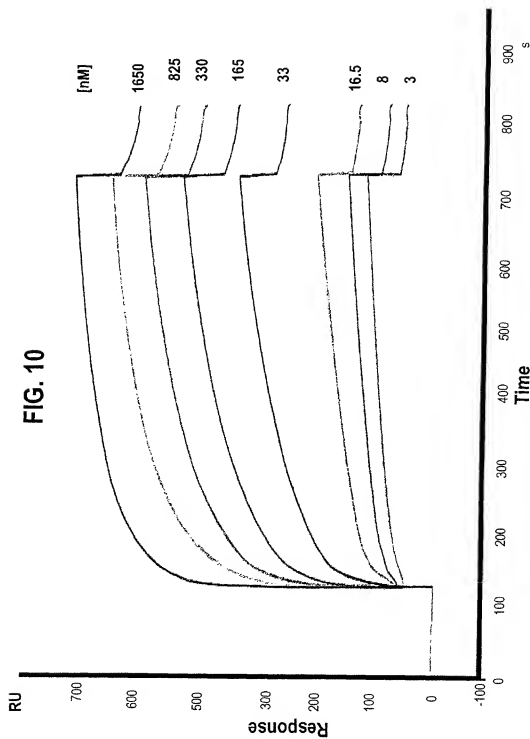




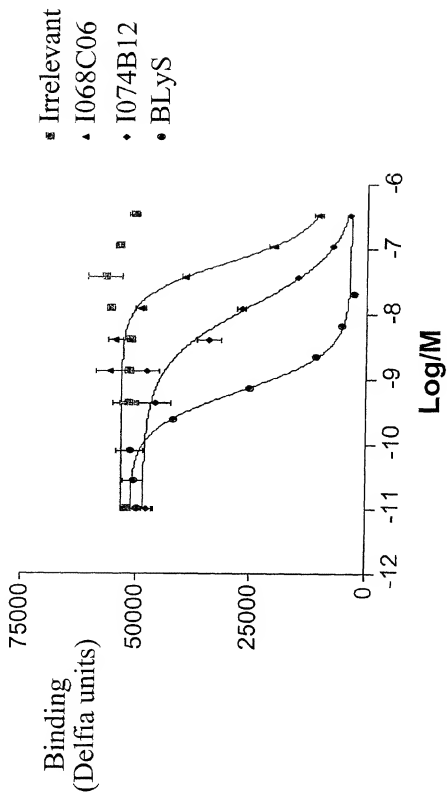
FIG. 8

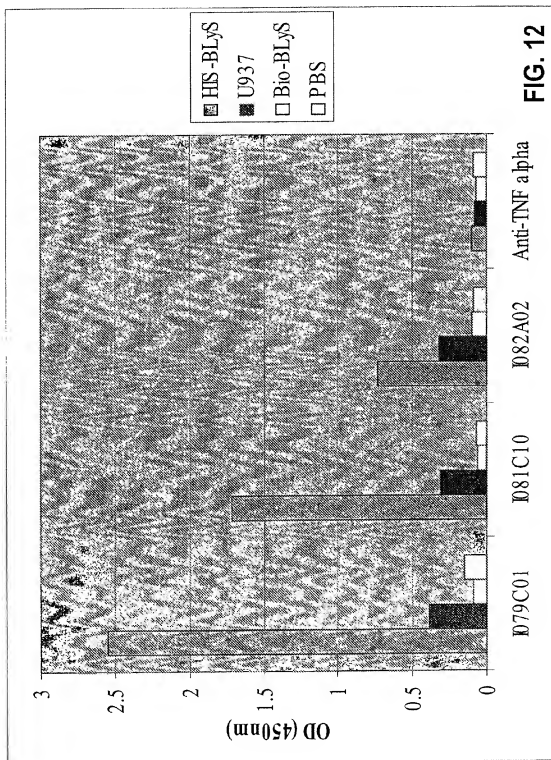


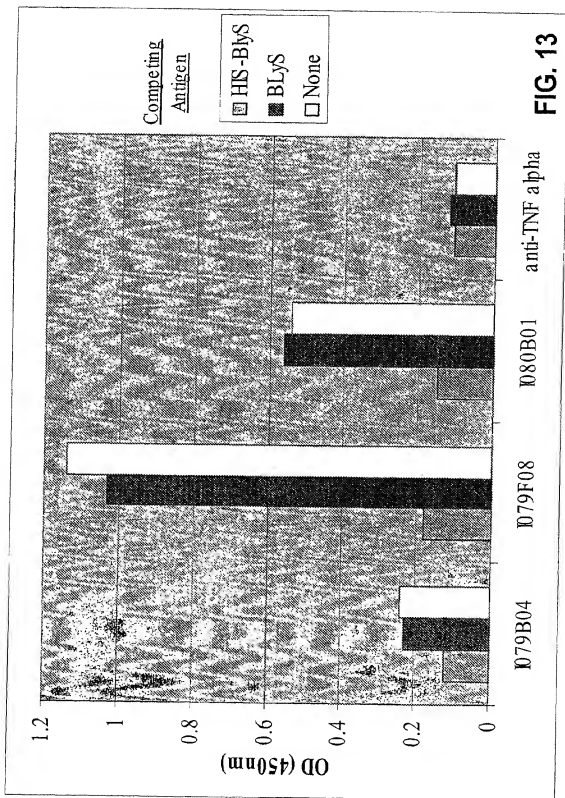




**FIG. 11**  
**Scfvs to soluble BLYS only**







**FIG. 14**  
**Plate 1079 Sensorgram - 8 Clones**

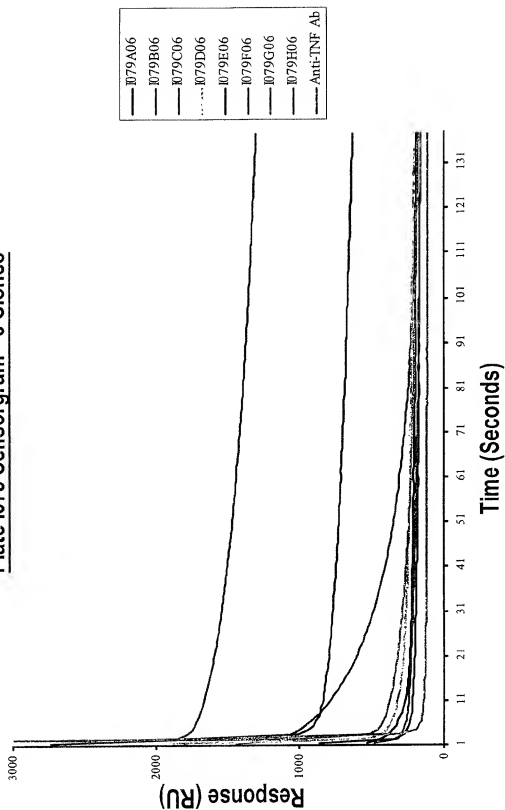
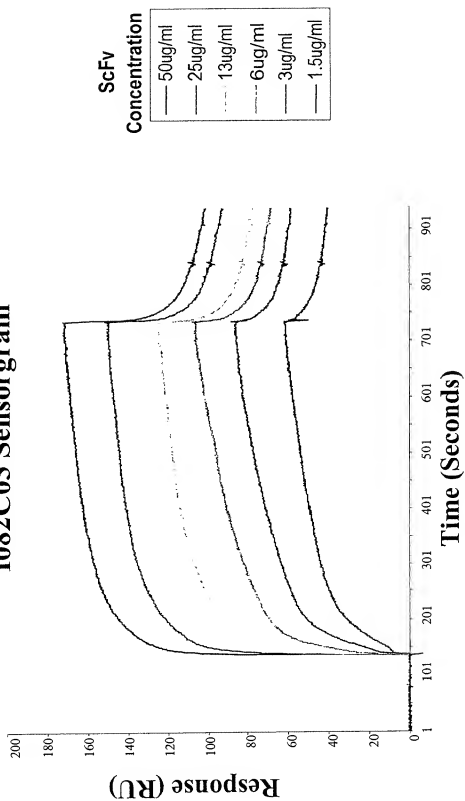


FIG. 15

## I082C03 Sensorgram





## P388 Competition ELISA

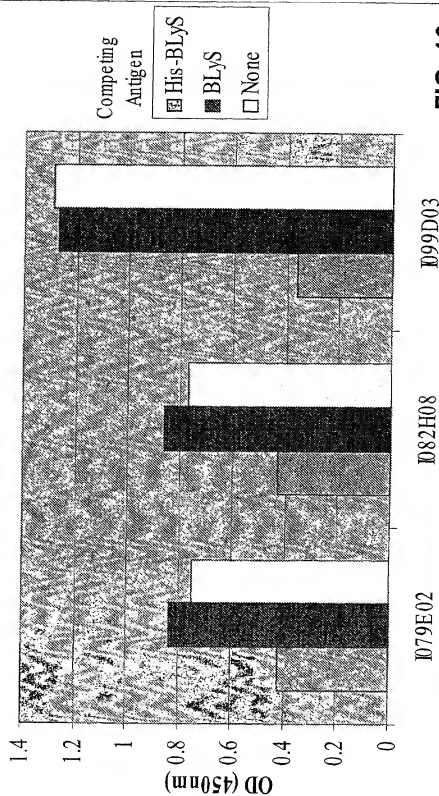


FIG. 16

# 1

## ANTIBODIES THAT IMMUNOSPECIFICALLY BIND BLYS

### INTRODUCTION

The present invention relates to antibodies and related molecules that immunospecifically bind to B Lymphocyte Stimulator (BlyS<sup>TM</sup>) protein. The present invention also relates to methods and compositions for detecting, diagnosing, or prognosing a disease or disorder associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate function of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor, comprising antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to B Lymphocyte Stimulator. The present invention further relates to methods and compositions for preventing, treating or ameliorating a disease or disorder associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate B Lymphocyte Stimulator function or B Lymphocyte Stimulator receptor function, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to B Lymphocyte Stimulator.

### BACKGROUND OF THE INVENTION

B Lymphocyte Stimulator (BlyS<sup>TM</sup>) protein is a member of the tumor necrosis factor ("TNF") superfamily that induces both *in vivo* and *in vitro* B cell proliferation and differentiation (Moore et al., Science 285: 260-263 (1999)). B Lymphocyte Stimulator is distinguishable from other B cell growth and differentiation factors such as IL-2, IL-4, IL-5, IL-6, IL-7, IL-13, IL-15, CD40L, or CD27L (CD70) by its monocyte-specific gene and protein expression pattern and its specific receptor distribution and biological activity on B lymphocytes. B Lymphocyte Stimulator expression is not detected on natural killer ("NK") cells, T cells or B cells, but is restricted to cells of myeloid origin. B Lymphocyte Stimulator expression on resting monocytes is upregulated by interferon-gamma (IFN-gamma). The gene encoding B Lymphocyte Stimulator has been mapped to chromosome 13q34.

B Lymphocyte Stimulator is expressed as a 285 amino acid type II membrane-bound polypeptide and a soluble 152 amino acid polypeptide (Moore et al., 1999 supra). The membrane-bound form of B Lymphocyte Stimulator has a predicted transmembrane spanning domain between amino acid residues 47 and 73. The NH<sub>2</sub>-terminus of the soluble form of B Lymphocyte Stimulator begins at Ala<sup>134</sup> of the membrane-bound form of B Lymphocyte Stimulator. Soluble recombinant B Lymphocyte Stimulator has been shown to induce *in vitro* proliferation of murine splenic B cells and to bind to a cell-surface receptor on these cells (Moore et al., 1999 supra). Soluble B Lymphocyte Stimulator administration to mice has been shown to result in an increase in the proportion of CD45R<sup>du</sup> Ly6D<sup>bright</sup> (also known as ThB) B cells and an increase in serum IgM and IgA levels (Moore et al., 1999 supra). Thus, B Lymphocyte Stimulator displays a B cell tropism in both its receptor distribution and biological activity.

Based upon its expression pattern and biological activity, B Lymphocyte Stimulator has been suggested to be involved in the exchange of signals between B cells and monocytes or their differentiated progeny. The restricted expression patterns of B Lymphocyte Stimulator receptor and ligand

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suggest that B Lymphocyte Stimulator may function as a regulator of T cell-independent responses in a manner analogous to that of CD40 and CD40L in T cell-dependent antigen activation. As such, antibodies and related molecules that immunospecifically bind to B Lymphocyte Stimulator may find medical utility in, for example, the treatment of B cell disorders associated with autoimmunity, neoplasia, or immunodeficiency syndromes.

### SUMMARY OF THE INVENTION

The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of B Lymphocyte Stimulator. In particular, the invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of human B Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or B Lymphocyte Stimulator expressed on human monocytes; murine B Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or B Lymphocyte Stimulator expressed on murine monocytes; rat B Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey B Lymphocyte Stimulator (e.g., the monkey B Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey B Lymphocyte Stimulator, or B Lymphocyte Stimulator expressed on monkey monocytes), preferably human B Lymphocyte Stimulator. The present invention also encompasses methods and compositions for detecting, diagnosing, or prognosing diseases or disorders associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate function of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, use of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator. Diseases and disorders which can be detected, diagnosed, or prognosed with the antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention include, but are not limited to, immune disorders (e.g., lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (e.g., asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (e.g., AIDS), and proliferative disorders (e.g., leukemia, carcinoma, and lymphoma). The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate function of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, administering to said animal an effective amount of one or more antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator. Diseases and disorders which can be prevented, treated or ameliorated by administering an effective amount of an antibody of the invention include, but are not limited to,

immune disorders (e.g., lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (e.g., asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (e.g., AIDS), and proliferative disorders (e.g., leukemia, carcinoma, and lymphoma).

Using phage display technology, the present inventors have identified single chain antibody molecules ("scFvs") that immunospecifically bind to B Lymphocyte Stimulator, including scFvs that immunospecifically bind to soluble B Lymphocyte Stimulator, scFvs that immunospecifically bind the membrane-bound form of B Lymphocyte Stimulator, and scFvs that immunospecifically bind to both the soluble form and the membrane-bound form of B Lymphocyte Stimulator. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

In particular, the invention relates to scFvs comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-2128, preferably SEQ ID NOS: 834-872, 1570-1595, and 1886-1908, and most preferably SEQ ID NOS: 1-46, 321-329, 1563-1569, and 1881-1885, as referred to in Table 1 below. In specific embodiments, the present invention relates to scFvs that immunospecifically bind the soluble form of B Lymphocyte Stimulator, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1563-1569, preferably SEQ ID NOS: 1570-1595, and most preferably SEQ ID NOS: 1563-1569, as referred to in Table 1, below. In other embodiments, the present invention also relates to scFvs that immunospecifically bind the membrane-bound form of B Lymphocyte Stimulator, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1881-2128, preferably SEQ ID NOS: 1886-1908, and most preferably SEQ ID NOS: 1881-1885, as referred to in Table 1 below. The present invention further relates to scFvs that immunospecifically bind both the membrane-bound form and soluble form of B Lymphocyte Stimulator, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1-1562, preferably SEQ ID NOS: 834-872, and most preferably SEQ ID NOS: 1-46, and 321-329, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of B Lymphocyte Stimulator, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the variable heavy ("VH") domains referred to in

Table 1, below, or any one of the variable light ("VL") domains referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908, as referred to in Table 1 below. In another preferred embodiment, antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

The present invention also provides antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of B Lymphocyte Stimulator, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, below, and any one of the VL domains referred to in Table 1. In a preferred embodiment, the antibodies of the invention comprise or alternatively consist of, a polypeptide having the amino acid sequence of a VH and VL domain contained in the same scFv referred to in Table 1. In another preferred embodiment, antibodies of the present invention, comprise, or alternatively consist of, a VH domain from an scFv of SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908, as disclosed in Table 1, and a VL domain from an scFv of SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908, as disclosed in Table 1. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, the VH and VL domain from a single scFv of SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908, as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of B Lymphocyte Stimulator, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one, two, three or more of the VH complementarity determining regions ("CDRs") (i.e., VH CDR1, VH CDR2, or VH CDR3) referred to in Table 1 and/or any one, two, three or more of the VL CDRs (i.e., VL CDR1, VL CDR2, or VL CDR3) referred to in Table 1. In one embodiment, antibodies of the present invention com-

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prise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1 and/or any one of the VL CDR1s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR2s referred to in Table 1 and/or any one of the VL CDR2s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR3s referred to in Table 1 and/or any one of the VL CDR3s referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

In another embodiment, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) immunospecifically bind to a polypeptide or polypeptide fragment of B Lymphocyte Stimulator, and comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1, any one of the VH CDR2s referred to in Table 1, and/or any one of the VH CDR3s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VL CDR1s referred to in Table 1, any one of the VL CDR2s referred to in Table 1, and/or any one of the VL CDR3s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, at least one, two, three, four, five, six, or more CDRs that correspond to the same scFv referred to in Table 1, more preferably where CDR1, CDR2, and CDR3 of the VL domain correspond to the same scFv or where CDR1, CDR2, and CDR3 of the VH domain correspond to the same scFv, and most preferably where all six CDRs correspond to the same scFv referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that: immunospecifically bind to the soluble form of B Lymphocyte Stimulator (e.g., a polypeptide consisting of amino acids 134-285 of SEQ ID NO:3228); that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator (e.g., a polypeptide consisting of amino acids 1-285 of SEQ ID NO:3228 or a B Lymphocyte Stimulator polypeptide expressed on the surface of monocytes) and/or that immunospecifically bind to both the soluble form and membrane-bound form of B Lymphocyte Stimulator. In a preferred embodiment, antibodies of the present invention immuno-

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specifically bind to the soluble form of B Lymphocyte Stimulator and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically bind to the soluble form of B Lymphocyte Stimulator. In another preferred embodiment, antibodies of the present invention immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator. In yet another preferred embodiment, antibodies of the present invention immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically binds to the soluble form and membrane-bound form of B Lymphocyte Stimulator. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a VH domain and a VL domain corresponding to the same scFv disclosed in Table 1, which antibodies immunospecifically bind to the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, or both the soluble form and membrane-bound form of B Lymphocyte Stimulator. Nucleic acid molecules encoding these antibodies are also encompassed by the invention. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

A VH domain of an amino acid sequence disclosed herein may be combined with

a VL domain of an amino acid sequence disclosed herein, or other VL domains, to provide a VH/VL pairing representing an antigen-binding site of an antibody. Similarly, a VL domain of an amino acid sequence disclosed herein may be combined with a VH domain of an amino acid sequence disclosed herein, or other VH domains. Further, one or more CDRs disclosed herein may be taken from a VH or VL domain and incorporated into a suitable framework as discussed infra.

The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof (including derivatives)) comprising, or alternatively consisting of, of VH domains, VL domains and/or CDRs described herein, which antibodies, immunospecifically bind to B Lymphocyte Stimulator (e.g., soluble B Lymphocyte Stimulator and membrane-bound B Lymphocyte Stimulator) and can be routinely assayed for immunospecific binding to B Lymphocyte Stimulator using methods known in the art, such as, for example, the immunoassays disclosed infra. Antibodies and antibody fragments or variants (including derivatives) of the invention may include, for example, one or more amino acid sequence alterations (addition, deletion, substitution and/or insertion of an amino acid residue). These alterations may be made in one or more framework regions and/or one or more CDR's.

The antibodies of the invention (including antibody fragments, and variants and derivative thereof) can be routinely made by methods known in the art. Molecules comprising, or alternatively consisting of, fragments or variants of any of the VH domains, VH CDRs, VL domains, and VL CDRs whose sequences are specifically disclosed herein may be employed in accordance with the present invention. Nucleic acid molecules encoding these antibodies and molecules (including fragments, variants, and derivatives) are also encompassed by the invention.

The present invention also provides panels of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) wherein the panel members correspond to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, F(ab')<sub>2</sub> fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antidiotypic (anti-Id) antibodies, and scFvs). The present invention further provides mixtures of antibodies, wherein the mixture corresponds to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, F(ab')<sub>2</sub> fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antidiotypic (anti-Id) antibodies, and scFvs). The present invention also provides for compositions comprising, or alternatively consisting of, one, two, three, four, five, ten, fifteen, twenty, or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). A composition of the invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty, or more amino acid sequences of one or more antibodies or fragments or variants thereof. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one or more antibodies of the invention.

The present invention also provides for fusion proteins comprising an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention, and a heterologous polypeptide (i.e., a polypeptide unrelated to an antibody or antibody domain). Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention. A composition of the present invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention.

The present invention also provides for a nucleic acid molecule, generally

isolated, encoding an antibody (including molecules such as scFvs, which comprise, or alternatively consist of, an antibody fragment or variant thereof) of the invention. The present invention also provides a host cell transformed with a nucleic acid molecule of the invention and progeny thereof. The present invention also provides a method for the production of an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention. The present invention further provides a method of expressing an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention from a nucleic acid molecule. These and other aspects of the invention are described in further detail below.

The present invention also encompasses methods and compositions for detecting, diagnosing and/or prognosing

diseases or disorders associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor function in an animal, preferably a mammal, and most preferably a human, comprising using antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator. Diseases and disorders which can be detected, diagnosed or prognosed with the antibodies of the invention include, but are not limited to, immune disorders (e.g., lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (e.g., asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (e.g., AIDS), and proliferative disorders (e.g., leukemia, carcinoma, and lymphoma).

In specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies). In other specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypogammaglobulinemia (e.g., an immunodeficiency).

The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor function in an animal, preferably a mammal, and most preferably a human, comprising administering to said animal an effective amount of one or more antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator. Diseases and disorders which can be prevented, treated or inhibited by administering an effective amount of one or more antibodies or molecules of the invention include, but are not limited to, immune disorders (e.g., lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (e.g., asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (e.g., AIDS), and proliferative disorders (e.g., leukemia, carcinoma, and lymphoma).

In specific embodiments, the present invention encompasses methods and compositions (e.g., antagonist anti-B Lymphocyte Stimulator antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiency syndromes). In other specific embodiments, the present invention encompasses methods and compositions (e.g., agonist anti-B Lymphocyte Stimulator antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypogammaglobulinemia (e.g., an immunodeficiency syndrome).

Autoimmune disorders, diseases, or conditions that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmune thrombocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polyneuropathy, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura

(e.g., Henoch-Schönlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis, systemic lupus erythematosus, discoid lupus, Goodpasture's syndrome, Pemphigus, Receptor autoimmunities such as, for example, (a) Graves' Disease, (b) Myasthenia Gravis, and (c) insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, scleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia, idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjögren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiomyopathy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders).

Immunodeficiencies that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia/aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

#### Definitions

The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. As such, the term antibody encompasses not only whole antibody molecules, but also antibody fragments as well as variants (including derivatives) of antibodies and antibody fragments. Examples of molecules which are described by the term "antibody" in this application include, but are not limited to: single chain Fvs (scFvs), Fab fragments, Fab' fragments, F(ab')<sub>2</sub>, disulfide linked Fvs (sdFvs), Fvs, and fragments comprising or alternatively consisting of, either a

VL or a VH domain. The term "single chain Fv" or "scFv" as used herein refers to a polypeptide comprising a VL domain of antibody linked to a VH domain of an antibody. Antibodies that immunospecifically bind to B Lymphocyte Stimulator may have cross-reactivity with other antigens. Preferably, antibodies that immunospecifically bind to B Lymphocyte Stimulator do not cross-react with other antigens. Antibodies that immunospecifically bind to B Lymphocyte Stimulator can be identified, for example, by immunoassays or other techniques known to those of skill in the art, e.g., the immunoassays described in the Examples below.

Antibodies of the invention include, but are not limited to, monoclonal, multispecific, human or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub>, IgG<sub>4</sub>, IgA<sub>1</sub> and IgA<sub>2</sub>) or subclass of immunoglobulin molecule. Preferably, an antibody of the invention comprises, or alternatively consists of, a VH domain, VH CDR, VL domain, or VL CDR having an amino acid sequence of any one of those referred to in Table I, or a fragment or variant thereof.

An antibody of the invention "which binds the soluble form of B Lymphocyte Stimulator" is one which binds the 152 amino acid soluble form of the B Lymphocyte Stimulator protein (amino acids 134-285 of SEQ ID NO:3228). In specific embodiments of the invention, an antibody of the invention "which binds the soluble form of B Lymphocyte Stimulator" does not also bind the membrane-bound or membrane-associated form of B Lymphocyte Stimulator. Assays which measure binding to the soluble form of B Lymphocyte Stimulator include, but are not limited to, receptor binding inhibition assay or capture of soluble B Lymphocyte Stimulator from solution as described in Examples 8 and 9.

An antibody of the invention "which binds the membrane-bound form of B Lymphocyte Stimulator" is one which binds the membrane-associated (uncleaved) B Lymphocyte Stimulator protein. In specific embodiments of the invention, an antibody of the invention "which binds the membrane-bound form of B Lymphocyte Stimulator" does not also bind the soluble form of B Lymphocyte Stimulator. In an ELISA is an indicator that an antibody binds the membrane-bound form of B Lymphocyte Stimulator, but should not be relied upon as proof of specificity for the membrane-bound form of B Lymphocyte Stimulator. Assays that may be relied upon as proof of an antibody's specificity for membrane-bound B Lymphocyte Stimulator, include, but are not limited to, binding to plasma membranes expressing B Lymphocyte Stimulator as described in Example 2. An antibody of the invention "which binds both the soluble form and the membrane-bound form of B Lymphocyte Stimulator" is one which binds both the membrane-bound form and the soluble form of B Lymphocyte Stimulator.

The term "variant" as used herein refers to a polypeptide that possesses a similar or identical function as a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody or antibody fragment thereof, but does not necessarily comprise a similar or identical amino acid sequence of a B Lymphocyte Stimulator polypeptide, a fragment of B Lym-

phocyte Stimulator, an anti-B Lymphocyte Stimulator antibody or antibody fragment thereof, or possess a similar or identical structure of a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody or antibody fragment thereof. A variant having a similar amino acid refers to a polypeptide that satisfies at least one of the following: (a) a polypeptide comprising, or alternatively consisting of, an amino acid sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% identical to the amino acid sequence of a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody or antibody fragment thereof (including a VH domain, VHCDC, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1) described herein; (b) a polypeptide encoded by a nucleotide sequence, the complementary sequence of which hybridizes under stringent conditions to a nucleotide sequence encoding a B Lymphocyte Stimulator polypeptide (e.g., SEQ ID NO:3228), a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody or antibody fragment thereof (including a VH domain, VHCDC, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1), described herein, of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino acid residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues; and (c) a polypeptide encoded by a nucleotide sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99%, identical to the nucleotide sequence encoding a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody or antibody fragment thereof (including a VH domain, VHCDC, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1), described herein. A polypeptide with similar structure to a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody or antibody fragment thereof, described herein refers to a polypeptide that has a similar secondary, tertiary or quaternary structure of a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody, or antibody fragment thereof, described herein. The structure of a polypeptide can be determined by methods known to those skilled in the art, including but not limited to, X-ray crystallography, nuclear magnetic resonance, and crystallographic electron microscopy.

To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide at the corresponding position in the second

sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity = number of identical overlapping positions / total number of positions × 100%). In one embodiment, the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm known to those of skill in the art. An example of a mathematical algorithm for comparing two sequences is the algorithm of Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 87:2264-2268(1990), modified as in Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 90:5873-5877(1993). The BLASTn and BLASTx programs of Altschul, et al. *J. Mol. Biol.* 215:403-410(1990) have incorporated such an algorithm. BLAST nucleotide searches can be performed with the BLASTn program, score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTx program, score=50, wordlength=3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. *Nucleic Acids Res.* 25:3389-3402(1997). Alternatively, PSI-BLAST can be used to perform an iterated search which detects distant relationships between molecules (id.). When utilizing BLAST, Gapped BLAST, and PSI-BLAST programs, the default parameters of the respective programs (e.g., BLASTx and BLASTn) can be used. (See <http://www.ncbi.nlm.nih.gov>.)

Another example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). The ALIGN program (version 2.0) which is part of the GCG sequence alignment software package has incorporated such an algorithm. Other algorithms for sequence analysis known in the art include ADVANCE and ADAM as described in Torelli and Robotti *Comput. Appl. Biosci.*, 10: 3-5(1994); and FASTA described in Pearson and Lipman *Proc. Natl. Acad. Sci.* 85:2444-8 (1988). Within FASTA, ktup is a control option that sets the sensitivity and speed of the search.

The term "derivative" as used herein, refers to a variant polypeptide of the invention that comprises, or alternatively consists of, an amino acid sequence of a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, or an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator, which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an antibody that immunospecifically binds to B Lymphocyte Stimulator which has been modified, e.g., by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, or an anti-B Lymphocyte Stimulator antibody, may be modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. A derivative of a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, or an anti-B Lymphocyte Stimulator antibody, may be modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to, specific chemical cleavage, acetylation, formylation, meta-

bolic synthesis of tunicamycin, etc. Further, a derivative of a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, or an anti-B Lymphocyte Stimulator antibody, may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, or an anti-B Lymphocyte Stimulator antibody, described herein.

The term "epitopes" as used herein refers to portions of B Lymphocyte Stimulator having antigenic or immunogenic activity in an animal, preferably a mammal. An epitope having immunogenic activity is a portion of B Lymphocyte Stimulator that elicits an antibody response in an animal. An epitope having antigenic activity is a portion of B Lymphocyte Stimulator to which an antibody immunospecifically binds as determined by any method known in the art, for example, by the immunoassays described herein. Antigenic epitopes need not necessarily be immunogenic.

The term "fragment" as used herein refers to a polypeptide comprising an amino acid sequence of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 35 amino acid residues, at least 40 amino acid residues, at least 45 amino acid residues, at least 50 amino acid residues, at least 60 amino acid residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, at least 150 amino acid residues, at least 175 amino acid residues, at least 200 amino acid residues, or at least 250 amino acid residues, of the amino acid sequence of B Lymphocyte Stimulator, or an anti-B Lymphocyte Stimulator antibody (including molecules such as scFv's, that comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically binds to B Lymphocyte Stimulator.

The term "fusion protein" as used herein refers to a polypeptide that comprises, or alternatively consists of, an amino acid sequence of an anti-B Lymphocyte Stimulator antibody of the invention and an amino acid sequence of a heterologous polypeptide (i.e., a polypeptide unrelated to an antibody or antibody domain).

The term "host cell" as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

#### DESCRIPTION OF THE FIGURES

FIG. 1. ELISA results for three scFvs, I006E07, I008D05 and I016F04, that immunospecifically bind to U937 membranes, but not to bind to or cross-react with TNF-alpha or BSA.

FIG. 2. The results for three scFvs, I016H07, I001C09 and I018D07, in a receptor inhibition assay.

FIG. 3. ELISA results for two scFvs (I022D01 and I031F02) demonstrating their ability to bind to human B Lymphocyte Stimulator and to cross-react with mouse B Lymphocyte Stimulator, but not to bind to or cross-react with other antigens of the TNF ligand family.

FIG. 4. ELISA results for three scFvs (I031F09, I050A12, and I051C04) binding to U937 plasma membranes when either B Lymphocyte Stimulator or TNF-alpha is used as a competitor.

FIG. 5. Kinetic analysis of scFv antibody I003C02. A dilution series of I003C02 from 3 nM to 825 nM is shown. Association and dissociation curves were generated using a BIAcore 2000 and BIAevaluation 3.0 software.

FIG. 6. Typical titration curves for two scFv antibodies (I007F11 and I050A07) are shown in FIG. 6. Unlabelled B Lymphocyte Stimulator competed for binding to its receptor with an  $IC_{50}$  value of 0.8 nM. The  $IC_{50}$  values for I007F11 and I050A07 are 7.9 nM and 17.1 nM, respectively. The assay was performed in triplicate and standard error bars are shown.

FIG. 7. ELISA results for three scFvs clones (I074B12, I075F12 and I075A02) that immunospecifically bind to immobilized B Lymphocyte Stimulator, but not to U937 plasma membranes, TNF-alpha or BSA. As a control, a phage antibody that recognizes TNF $\alpha$ , is also shown in FIG. 7.

FIG. 8. The results for two scFvs (I025B09 and I026C04) in a receptor inhibition assay.

FIG. 9. ELISA results for two scFvs clones (I067F05 and I078D02) demonstrating their ability to bind to immobilized human B Lymphocyte Stimulator and to cross-react with immobilized mouse B Lymphocyte Stimulator, but not to bind to or cross-react with other antigens of the TNF ligand family.

As a control, a phage antibody that recognizes TNF $\alpha$ , is also shown in FIG. 7.

FIG. 10. Kinetic analysis of scFv antibody I002A01. A dilution series of I002A01 from 3 nM to 1650 nM is shown. Association and dissociation curves were generated using a BIAcore 2000 and BIAevaluation 3.0 software.

FIG. 11. Typical titration curves for two scFvs, I0068C06 and I074B12, are shown in FIG. 11. Unlabelled B Lymphocyte Stimulator competed for binding to its receptor with an inhibitory constant 50 ( $IC_{50}$ ) value of 0.66 nM. The  $IC_{50}$  values for I0068C06 and I074B12 are 61 nM and 13 nM, respectively. The assay was performed in triplicate and standard error bars are shown.

FIG. 12. ELISA results for three clones (I079C01, I081C10 and I082A02) demonstrating their ability to bind histidine-tagged B Lymphocyte Stimulator, U937 plasma membranes, but not to bind immobilized biotinylated B Lymphocyte Stimulator.

FIG. 13. ELISA results for three scFvs (I079B04, I079F08, and I080B01) binding to U937 plasma membranes when either histidine-tagged B Lymphocyte Stimulator or biotinylated B Lymphocyte Stimulator is used as a competitor.

FIG. 14. An example of the dissociation section of a typical sensorgram for 8 scFvs is shown in FIG. 14. An anti-TNF $\alpha$  antibody that does not recognize B Lymphocyte Stimulator was included as a control. Of the 8 scFvs exemplified, I079F06 was identified for further study due to the relatively high numbers of RU's bound to the surface.

FIG. 15. A typical example of the binding curves generated for the scFv antibody I082C03 is shown in FIG. 15. The off-rate for this clone was calculated as  $2 \times 10^{-3} \text{ s}^{-1}$ . The affinity of I082C03 was calculated as 20 nM, assuming 100% activity of the scFv.

FIG. 16. ELISA results for three scFvs (I079B04, I079F08, and I080B01) binding to P388 plasma membranes when either histidine-tagged B Lymphocyte Stimulator or biotinylated B Lymphocyte Stimulator is used as a competitor.



## DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator or a fragment or variant of B Lymphocyte Stimulator. In particular, the invention provides antibodies such as, for example, single chain Fvs (scFvs) having an amino acid sequence of any one of SEQ ID NOS:1-2128, as referred to in Table 1. In particular, the present invention encompasses antibodies that immunospecifically bind to a polypeptide, a polypeptide fragment or variant, or an epitope of human B Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or B Lymphocyte Stimulator expressed on human monocytes; murine B Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or B Lymphocyte Stimulator expressed on murine monocytes; rat B Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey B Lymphocyte Stimulator (e.g., the monkey B Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey B Lymphocyte Stimulator, or B Lymphocyte Stimulator expressed on monkey monocytes) (as determined by immunoassays known in the art for assaying specific antibody-antigen binding).

The polypeptide sequence shown in SEQ ID NO:3228 was obtained by sequencing and translating the cDNA of the HNEDU15 clone which was deposited on Oct. 22, 1996 at the American Type Culture Collection, 10801 University Boulevard, Manassas, Va. 20110-2209, and assigned ATCC<sup>TM</sup> Accession No. 97768. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, Calif.). The ATCC<sup>TM</sup> deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

The polypeptide sequence shown in SEQ ID NO:3229 was obtained by sequencing and translating the cDNA of the HDPMC52 clone, which was deposited on Dec. 10, 1998 at the American Type Culture Collection, and assigned ATCC<sup>TM</sup> Accession No. 203518. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, Calif.). The ATCC<sup>TM</sup> deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

The B Lymphocyte Stimulator polypeptides bound by the antibodies of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to antibodies that bind monomers and multimers of the B Lymphocyte Stimulator polypeptides of the invention, their preparation, and compositions (preferably, pharmaceutical compositions) containing them. In specific embodiments, the antibodies of the invention bind B Lymphocyte Stimulator monomers, dimers, trimers or tetramers. In additional embodiments, the antibodies of the invention bind at least dimers, at least trimers, or at least tetramers of B Lymphocyte Stimulator.

Multimeric B Lymphocyte Stimulator bound by the antibodies of the invention may be homomers or heteromers. A B Lymphocyte Stimulator homomer, refers to a multimer containing only B Lymphocyte Stimulator polypeptides (including B Lymphocyte Stimulator fragments, variants, and fusion proteins, as described herein). These homomers may contain B Lymphocyte Stimulator polypeptides having iden-

tical or different amino acid sequences. In specific embodiments, the antibodies of the invention bind a B Lymphocyte Stimulator homodimer (e.g., containing two B Lymphocyte Stimulator polypeptides having identical or different amino acid sequences) or a B Lymphocyte Stimulator homotrimer (e.g., containing three B Lymphocyte Stimulator polypeptides having identical or different amino acid sequences). In a preferred embodiment, the antibodies of the invention bind homotrimers of B Lymphocyte Stimulator. In additional embodiments, the antibodies of the invention bind a homomeric B Lymphocyte Stimulator multimer which is at least a homodimer, at least a homotrimer, or at least a homotetramer.

Heteromeric B Lymphocyte Stimulator refers to a multimer containing heterologous polypeptides (i.e., polypeptides of a different protein) in addition to the B Lymphocyte Stimulator polypeptides of the invention. In a specific embodiment, the antibodies of the invention bind a B Lymphocyte Stimulator heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the antibodies of the invention bind a heteromeric B Lymphocyte Stimulator multimer which is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer. In highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising both B Lymphocyte Stimulator polypeptides and APRIL polypeptides (SEQ ID NO:3239; GenBank Accession No. AF046888; PCT International Publication Number WO97/33902; J. Exp. Med. 188(6):1185-1190) or fragments or variants thereof. In other highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising one B Lymphocyte Stimulator polypeptide (including fragments or variants) and two APRIL polypeptides (including fragments or variants). In still other highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising two B Lymphocyte Stimulator polypeptides (including fragments or variants) and one APRIL polypeptide (including fragments or variants). In a further nonexclusive embodiment, the heteromers bound by the antibodies of the invention contain CD40 ligand polypeptide sequence(s), or biologically active fragment(s) or variant(s) thereof.

In particularly preferred embodiments, the antibodies of the invention bind homomeric, especially homotrimeric, B Lymphocyte Stimulator polypeptides, wherein the individual protein components of the multimers consist of the mature form of B Lymphocyte Stimulator (e.g., amino acid residues 134-285 of SEQ ID NO:3228, or amino acid residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof. In other specific embodiments, antibodies of the invention bind heteromeric, especially heterotrimeric, B Lymphocyte Stimulator polypeptides such as a heterotrimer containing two B Lymphocyte Stimulator polypeptides and one APRIL polypeptide or a heterotrimer containing one B Lymphocyte Stimulator polypeptide and two APRIL polypeptides, and wherein the individual protein components of the B Lymphocyte Stimulator heteromer consist of the mature extracellular soluble portion of either B Lymphocyte Stimulator (e.g., amino acid residues 134-285 of SEQ ID NO:3228, or amino acid residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof, or the mature extracellular soluble portion APRIL (e.g., amino acid residues 105-250 of SEQ ID NO:3239) or fragments or variants thereof.

In specific embodiments, the antibodies of the invention bind conformational epitopes of a B Lymphocyte Stimulator monomeric protein. In specific embodiments, the antibodies of the invention bind conformational epitopes of a B Lym-

phocyte Stimulator multimeric, especially trimeric, protein. In other embodiments, antibodies of the invention bind conformational epitopes that arise from the juxtaposition of B Lymphocyte Stimulator with a heterologous polypeptide, such as might be present when B Lymphocyte Stimulator forms heterotrimers (e.g., with APRIL polypeptides (e.g., SEQ ID SEQ ID NO:3239)), or in fusion proteins between B Lymphocyte Stimulator and a heterologous polypeptide.

B Lymphocyte Stimulator multimers bound by the antibodies of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, B Lymphocyte Stimulator multimers, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, B Lymphocyte Stimulator heteromultimers, such as, for example, B Lymphocyte Stimulator heterotrimers or B Lymphocyte Stimulator heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, B Lymphocyte Stimulator multimers are formed by covalent associations with and/or between the B Lymphocyte Stimulator polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:3228 or SEQ ID NO:3229). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a B Lymphocyte Stimulator fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein (see, e.g., U.S. Pat. No. 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a B Lymphocyte Stimulator-Fc fusion protein. In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another TNF family ligand/receptor member that is capable of forming covalently associated multimers, such as for example, osteopontin (see, e.g., International Publication No. WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from CD40L, or a soluble fragment thereof. In another embodiment, two or B Lymphocyte Stimulator polypeptides are joined through synthetic linkers (e.g., peptide, carbohydrate or soluble polymer linkers). Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple B Lymphocyte Stimulator polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology.

In one embodiment, antibodies of the invention immunospecifically bind a B Lymphocyte Stimulator polypeptide having the amino acid sequence of SEQ ID NO:3228 or as encoded by the cDNA clone contained in ATCC™ No. 97768, or a polypeptide comprising a portion (i.e., a fragment) of the above polypeptides. In another embodiment, the invention provides an antibody that binds an isolated B

Lymphocyte Stimulator polypeptide having the amino acid sequence of SEQ ID NO:3229 or the amino acid sequence encoded by the cDNA clone contained in ATCC™ No. 203518, or an antibody that binds polypeptide comprising a portion (i.e., fragment) of the above polypeptides.

Antibodies of the present invention immunospecifically bind to polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCC™ accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCC™ accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

Additionally, antibodies of the present invention bind polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCC™ accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCC™ accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

In addition, antibodies of the invention bind polypeptides or polypeptide fragments comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NOS: 3230 through 3237.

In specific embodiments, the antibodies of the present invention immunospecifically bind polypeptide fragments including polypeptides comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NO:3228, encoded by the cDNA contained in the deposited clone, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments that may be bound by the antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, and/or 251 to 285 of SEQ ID NO:3228. Moreover, polypeptide fragments can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length.

In specific embodiments, antibodies of the present invention bind polypeptide fragments comprising, or alternatively consisting of, amino acid residues: 1-46, 31-44, 47-72, 73-285, 73-83, 94-102, 148-152, 166-181, 185-209, 210-221, 226-237, 244-249, 253-265, and/or 277-285 of SEQ ID NO:3228.

It will be recognized by one of ordinary skill in the art that mutations targeted to regions of a B Lymphocyte Stimulator polypeptide of SEQ ID NO:3228 which encompass the nineteen amino acid residue insertion which is not found in the B Lymphocyte Stimulator polypeptide sequence of SEQ ID NO:3229 (i.e., amino acid residues Val-142 through Lys-160 of the sequence of SEQ ID NO:3229) may affect the

observed biological activities of the B Lymphocyte Stimulator polypeptide. More specifically, a partial, non-limiting and non-exclusive list of such residues of the B Lymphocyte Stimulator polypeptide sequence which may be targeted for mutation includes the following amino acid residues of the B Lymphocyte Stimulator polypeptide sequence as shown in SEQ ID NO:3228: V-142; T-143; Q-144; D-145; C-146; L-147; Q-148; L-149; I-150; A-151; D-152; S-153; E-154; T-155; P-156; T-157; I-158; Q-159; and K-160. Thus, in specific embodiments, antibodies of the present invention that bind B Lymphocyte Stimulator polypeptides which have one or more mutations in the region from V-142 through K-160 of SEQ ID NO:3228 are contemplated.

Polypeptide fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 15, 16-30, 31-46, 47-55, 56-72, 73-104, 105-163, 163-188, 186-210 and 210-284 of the amino acid sequence disclosed in SEQ ID NO:3228. Additional representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 143, 1-150, 47-143, 47-150, 73-143, 73-150, 100-150, 140-145, 142-148, 140-150, 140-200, 140-225, and 140-266 of the amino acid sequence disclosed in SEQ ID NO:3229. Moreover, polypeptide fragments that may be bound by antibodies of the present invention, can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini.

Additional preferred embodiments encompass antibodies that bind polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of B Lymphocyte Stimulator (e.g., amino acid residues 1-46 of SEQ ID NO:3228), the predicted transmembrane domain of B Lymphocyte Stimulator (e.g., amino acid residues 47-72 of SEQ ID NO:3228), the predicted extracellular domain of B Lymphocyte Stimulator (e.g., amino acid residues 73-285 of SEQ ID NO:3228), the mature soluble extracellular domain of B Lymphocyte Stimulator (e.g., amino acid residues 134-285 of SEQ ID NO:3228), the predicted TNF conserved domain of B Lymphocyte Stimulator (e.g., amino acids 191 to 284 of SEQ ID NO:3228), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the predicted extracellular domain of B Lymphocyte Stimulator (amino acid residues 1-46 fused to amino acid residues 73-285 of SEQ ID NO:3228).

Further additional preferred embodiments encompass polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of B Lymphocyte Stimulator (amino acid residues 1-46 of SEQ ID NO:3229), the predicted transmembrane domain of B Lymphocyte Stimulator (amino acid residues 47-72 of SEQ ID NO:3229), the predicted extracellular domain of B Lymphocyte Stimulator (amino acid residues 73-266 of SEQ ID NO:3229), the predicted TNF conserved domain of B Lymphocyte Stimulator (amino acids 172 to 265 of SEQ ID NO:3229), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the

predicted extracellular domain of B Lymphocyte Stimulator (amino acid residues 1-46 fused to amino acid residues 73-266 of SEQ ID NO:3229).

Certain additional embodiments of the invention encompass antibodies that bind polypeptide fragments comprising, or alternatively consisting of, the predicted beta-pleated sheet regions of the B Lymphocyte Stimulator polypeptides of SEQ ID NO:3228 and SEQ ID NO:3229. These polypeptide fragments comprising the beta-pleated sheets of B Lymphocyte Stimulator comprise, or alternatively consist of, amino acid residues Gln-144 to Ala-151, Phe-172 to Lys-173, Ala-177 to Glu-179, Asn-183 to Ile-185, Gly-191 to Lys-204, His-210 to Val-219, Leu-226 to Pro-237, Asn-242 to Ala-251, Gly-256 to Ile-263 and/or Val-276 to Leu-284 of SEQ ID NO:3228. In another, nonexclusive embodiment, these polypeptide fragments comprising the beta-pleated sheets of B Lymphocyte Stimulator comprise, or alternatively consist of, amino acid residues Phe-153 to Lys-154, Ala-158 to Glu-160, Asn-164 to Ile-166, Gly-172 to Lys-185, His-191 to Val-200, Leu-207 to Pro-218, Asn-223 to Ala-232, Gly-237 to Ile-244 and/or Val-257 to Leu-265 of SEQ ID NO:3229.

A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences of the invention includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228. Other combinations of amino acid sequences that may be bound by the antibodies of the invention may include the polypeptide fragments in an order other than that recited above (e.g., [Leu-114 to Thr-141] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] fused to [Val-142 to Lys-160] of (SEQ ID NO:3228). Other combinations of amino acid sequences that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-14 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228 fused to a FLAG tag; or [Met-1 to Lys-113] of SEQ ID NO:3228 fused to [Leu-114 to Thr-141] of SEQ ID NO:3228 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Val-142 to Lys-160] of SEQ ID NO:3228 fused to [Gly-161 to Gln-198] of SEQ ID NO:3228 fused to [Val-199 to Ala-248] of SEQ ID NO:3228 fused to [Gly-249 to Leu-285] of SEQ ID NO:3228).

A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; [Met-1 to Lys-113] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229. Other of amino acids

sequences that may be bound by the antibodies of the invention combinations may include the polypeptide fragments in an order other than that recited above (e.g., [Leu-114 to Thr-141] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] fused to [Gly-142 to Gln-179] of SEQ ID NO:3229). Other combinations of amino acid sequences that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229 fused to a FLAG tag (SEQ ID NO:3238) or, [Met-1 to Lys-113] of SEQ ID NO:3229 fused to [Leu-114 to Thr-141] of SEQ ID NO:3229 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Gly-142 to Gln-179] of SEQ ID NO:3229 fused to [Val-180 to Ala-229] of SEQ ID NO:3229 fused to [Gly-230 to Leu-266] of SEQ ID NO:3229.

Additional embodiments of the invention encompass antibodies that bind B Lymphocyte Stimulator polypeptide fragments comprising, or alternatively consisting of, functional regions of polypeptides of the invention, such as the Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and coil-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index set out in Tables 9 and 10 as described herein. In a preferred embodiment, the polypeptide fragments bound by the antibodies of the invention are antigenic (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of a complete (i.e., full-length) B Lymphocyte Stimulator polypeptide (e.g., SEQ ID NOS:3228 and 3229).

The data representing the structural or functional attributes of the B Lymphocyte Stimulator polypeptide of SEQ ID NO:3228 (Table 9) or the B Lymphocyte Stimulator polypeptide of SEQ ID NO:3229 (Table 10), as described above, was generated using the various modules and algorithms of the DNA\*STAR set on default parameters. Column I represents the results of a Garnier-Robson analysis of alpha helical regions; Column II represents the results of a Chou-Fasman analysis of alpha helical regions; Column III

represents the results of a Garnier Robson analysis of beta sheet regions; Column IV represents the results of a Chou-Fasman analysis of beta sheet regions; Column V represents the results of a Garnier Robson analysis of turn regions; Column VI represents the results of a Chou-Fasman analysis of turn regions; Column VII represents the results of a Garnier Robson analysis of coil regions; Column VIII represents a Kyte-Doolittle hydrophilicity plot; Column IX represents a Hopp-Woods hydrophobicity plot; Column X represents the results of an Eisenberg analysis of alpha amphipathic regions; Column XI represents the results of an Eisenberg analysis of beta amphipathic regions; Column XII represents the results of a Karplus-Schulz analysis of flexible regions; Column XIII represents the Jameson-Wolf antigenic index score; and Column XIV represents the Emini surface probability plot.

In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Tables 9 and 10 can be used to determine regions of the B Lymphocyte Stimulator polypeptide of SEQ ID NO:3228 (Table 9) or the B Lymphocyte Stimulator polypeptide of SEQ ID NO:3229 (Table 10) which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

The above-mentioned preferred regions set out in Tables 9 and 10 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in SEQ ID NO:2. As set out in Tables 9 and 10, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions. Preferably, antibodies of the present invention bind B Lymphocyte Stimulator polypeptides or B Lymphocyte Stimulator polypeptide fragments and variants comprising regions of B Lymphocyte Stimulator that combine several structural features, such as several (e.g., 1, 2, 3, or 4) of the same or different region features set out above and in Tables 9 and 10.

TABLE 9

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	.	.	.	.	.	0.73	-0.71	.	.	.	.	0.95	1.39
Asp	2	A	.	.	.	.	T	1.12	-0.66	*	.	.	.	1.15	1.56
Asp	3	A	.	.	.	.	T	1.62	-1.09	*	.	.	.	1.15	2.12
Ser	4	A	.	.	.	.	T	2.01	-1.51	*	.	.	.	1.15	4.19
Thr	5	A	.	.	.	.	T	2.40	-2.13	*	.	.	F	1.30	4.38
Glu	6	A	A	.	.	.	.	2.70	-1.73	*	.	F	F	0.90	4.51
Arg	7	A	A	.	.	.	.	2.81	-1.34	*	.	F	F	0.90	4.51
Glu	8	A	A	.	.	.	.	2.00	-1.73	*	.	F	F	0.90	6.12
Glu	9	A	.	.	.	.	.	1.99	-1.53	*	.	F	F	0.90	2.91
Ser	10	A	.	.	B	.	.	2.00	-1.04	*	.	F	F	0.90	2.15
Arg	11	A	.	.	B	.	.	1.33	-0.66	*	.	F	F	0.90	1.66
Leu	12	A	.	.	B	.	.	0.41	-0.09	*	.	F	F	0.45	0.51
Thr	13	A	.	.	B	.	.	0.46	0.20	*	.	F	F	-0.15	0.32
Ser	14	A	A	.	.	.	.	0.50	-0.19	*	.	.	.	0.30	0.32
Cys	15	A	A	.	.	.	.	0.91	-0.19	*	.	.	.	0.30	0.78
Leu	16	A	.	.	.	.	.	0.80	-0.87	*	.	.	.	0.90	1.06
Lys	17	A	A	.	.	.	.	1.61	-1.36	*	.	F	F	0.90	1.37
Lys	18	A	A	.	.	.	.	1.32	-1.74	*	.	F	F	0.90	4.44
Arg	19	A	.	.	.	.	.	1.67	-1.70	*	.	F	F	0.90	5.33
Glu	20	A	A	.	.	.	.	1.52	-2.39	*	.	F	F	0.90	5.33

TABLE 9-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Glu	21	A	A	.	.	.	.	.	2.38	-1.70	.	.	F	0.90	2.20
Met	22	A	A	.	.	.	.	.	2.23	-1.70	.	.	F	0.90	2.24
Lys	23	A	A	.	.	.	.	.	1.62	-1.70	.	.	F	0.90	2.24
Leu	24	A	A	.	.	.	.	.	0.66	-1.13	.	.	F	0.75	0.69
Lys	25	A	A	.	.	.	.	.	0.36	-0.49	.	.	F	0.45	0.52
Glu	26	A	A	.	B	.	.	.	-0.53	-0.71	.	.	.	0.60	0.35
Cys	27	A	A	.	B	.	.	.	-0.74	-0.03	.	.	.	0.30	0.30
Val	28	A	A	.	B	.	.	.	-1.00	-0.03	.	.	.	0.30	0.12
Ser	29	A	A	.	B	.	.	.	-0.08	0.40	.	.	.	-0.30	0.11
Ile	30	A	.	.	B	.	.	.	-0.08	0.40	.	.	.	-0.30	0.40
Leu	31	A	.	.	B	.	.	.	-0.08	-0.17	.	.	.	0.45	1.08
Pro	32	.	.	.	B	.	.	C	0.29	-0.81	.	.	F	1.10	1.39
Arg	33	.	.	.	T	.	.	.	0.93	-0.81	.	.	F	1.30	2.66
Lys	34	.	.	.	T	.	.	.	0.93	-1.07	.	.	F	1.84	4.98
Glu	35	.	.	.	.	T	.	C	0.97	-1.37	.	.	F	1.98	4.32
Ser	36	.	.	.	.	T	C	.	1.89	-1.16	.	.	F	2.52	1.64
Pro	37	.	.	.	.	T	C	.	1.80	-1.16	.	.	F	2.86	1.60
Ser	38	.	.	.	.	T	.	.	1.39	-0.39	.	.	F	3.40	1.24
Val	39	A	.	.	.	T	.	.	1.39	-0.77	.	.	F	2.36	1.24
Arg	40	A	.	.	.	.	.	.	1.39	-0.77	.	.	F	2.46	1.60
Ser	41	A	.	.	.	.	.	.	1.34	-1.20	.	.	F	2.46	2.00
Ser	42	.	.	.	.	T	T	.	1.60	-1.16	.	.	F	3.06	2.67
Lys	43	.	.	.	.	T	T	.	1.09	-1.80	.	.	F	3.06	2.72
Asp	44	.	.	.	.	T	T	.	1.13	-1.11	.	.	F	3.40	1.67
Gly	45	A	.	.	.	T	.	.	0.43	-0.81	.	.	F	2.66	1.03
Lys	46	A	A	.	.	.	.	.	0.14	-0.70	.	.	F	1.77	0.52
Leu	47	A	A	.	.	.	.	.	0.13	-0.20	.	.	.	0.98	0.31
Leu	48	A	A	.	.	.	.	.	-0.72	0.29	.	.	.	0.04	0.46
Ala	49	A	A	.	.	.	.	.	-1.53	0.54	.	.	.	-0.60	0.19
Ala	50	A	A	.	.	.	.	.	-2.00	1.23	.	.	.	-0.60	0.19
Thr	51	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.19
Leu	52	A	A	.	.	.	.	.	-2.63	1.04	.	.	.	-0.60	0.19
Leu	53	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.15
Leu	54	A	A	.	.	.	.	.	-2.34	1.41	.	.	.	-0.60	0.09
Ala	55	A	A	.	.	.	.	.	-2.42	1.31	.	.	.	-0.60	0.14
Leu	56	A	A	.	.	.	.	.	-2.78	1.20	.	.	.	-0.60	0.09
Leu	57	A	.	.	.	T	.	.	-2.78	1.09	.	.	.	-0.20	0.06
Ser	58	A	.	.	.	T	.	.	-2.28	1.09	.	.	.	-0.20	0.05
Cys	59	A	.	.	.	T	.	.	-2.32	1.07	.	.	.	-0.20	0.09
Cys	60	A	.	.	.	T	.	.	-2.59	1.03	.	.	.	-0.20	0.08
Leu	61	.	.	B	B	.	.	.	-2.08	0.99	.	.	.	-0.60	0.04
Thr	62	.	.	B	B	.	.	.	-1.97	0.99	.	.	.	-0.60	0.11
Val	63	.	.	B	B	.	.	.	-1.91	1.20	.	.	.	-0.60	0.17
Val	64	.	.	B	B	.	.	.	-1.24	1.39	.	.	.	-0.60	0.33
Ser	65	.	.	B	B	.	.	.	-1.43	1.10	.	.	.	-0.60	0.40
Phe	66	A	.	B	.	.	.	.	-1.21	1.26	.	.	.	-0.60	0.40
Tyr	67	A	.	B	.	.	.	.	-1.49	1.11	.	.	.	-0.60	0.54
Gln	68	A	.	B	.	.	.	.	-1.44	0.97	.	.	.	-0.60	0.41
Val	69	A	.	B	.	.	.	.	-0.59	1.27	.	.	.	-0.60	0.39
Ala	70	A	.	B	.	.	.	.	-0.63	0.89	.	.	.	-0.60	0.43
Ala	71	A	.	B	.	.	.	.	0.07	0.56	.	.	.	-0.60	0.25
Leu	72	A	.	.	.	T	.	.	-0.50	0.16	.	.	.	0.10	0.55
Glu	73	A	.	.	.	T	.	.	-1.09	0.20	.	.	F	0.25	0.45
Gly	74	A	.	.	.	T	.	.	-0.53	0.20	.	.	F	0.25	0.45
Asp	75	A	.	.	.	T	.	.	-0.76	0.09	.	.	F	0.25	0.73
Leu	76	A	A	.	.	.	.	.	-0.06	0.09	.	.	F	-0.15	0.35
Ala	77	A	A	.	.	.	.	.	0.17	-0.31	.	.	.	0.30	0.69
Ser	78	A	A	.	.	.	.	.	0.17	-0.24	.	.	.	0.30	0.42
Leu	79	A	A	.	.	.	.	.	-0.30	-0.24	.	.	.	0.30	0.88
Arg	80	A	A	.	.	.	.	.	-0.30	-0.24	.	.	.	0.30	0.72
Ala	81	A	A	.	.	.	.	.	0.17	-0.34	.	.	.	0.30	0.93
Glu	82	A	A	.	.	.	.	.	0.72	-0.30	.	.	.	0.45	1.11
Leu	83	A	A	.	.	.	.	.	0.99	-0.49	.	.	.	0.30	0.77
Gln	84	A	A	.	.	.	.	.	1.21	0.01	.	.	.	-0.15	1.04
Gly	85	A	A	.	.	.	.	.	1.10	0.01	.	.	.	-0.30	0.61
His	86	A	A	.	.	.	.	.	1.73	0.01	.	.	.	-0.15	1.27
His	87	A	A	.	.	.	.	.	0.92	-0.67	.	.	.	0.75	1.47
Ala	88	A	A	.	.	.	.	.	1.52	-0.39	.	.	.	0.45	1.22
Glu	89	A	A	.	.	.	.	.	0.93	-0.39	.	.	.	0.45	1.39
Lys	90	A	A	.	.	.	.	.	0.93	-0.39	.	F	.	0.60	1.03
Leu	91	A	.	.	.	T	.	.	0.38	-0.46	.	.	.	0.85	1.01
Pro	92	A	.	.	.	T	.	.	0.07	-0.46	.	.	.	0.70	0.59
Ala	93	A	.	.	.	T	.	.	0.07	-0.03	.	.	.	0.70	0.29
Gly	94	A	.	.	.	T	.	.	-0.14	0.47	.	.	.	-0.20	0.36
Ala	95	A	.	.	.	.	.	.	-0.14	0.21	.	.	.	-0.10	0.36
Gly	96	A	.	.	.	.	.	.	0.08	-0.21	.	F	.	0.65	0.71
Ala	97	A	.	.	.	.	.	.	-0.06	-0.21	.	F	.	0.65	0.72

TABLE 9-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Pro	98	A	.	.	.	.	.	.	-0.28	-0.21	.	*	F	0.65	0.71
Lys	99	A	A	.	.	.	.	.	0.07	-0.03	.	.	F	0.45	0.59
Ala	100	A	A	.	.	.	.	.	0.66	-0.46	.	.	F	0.60	1.01
Gly	101	A	A	.	.	.	.	.	0.41	-0.96	.	.	F	0.90	1.13
Leu	102	A	A	.	.	.	.	.	0.79	-0.89	.	.	F	0.75	0.57
Glu	103	A	A	.	.	.	.	.	0.41	-0.46	*	.	F	0.45	0.88
Glu	104	A	A	.	.	.	.	.	-0.49	-0.46	*	.	F	0.45	0.89
Ala	105	A	A	.	.	.	.	.	-0.21	-0.24	.	.	.	0.30	0.81
Pro	106	A	A	.	.	.	.	.	-0.46	-0.44	.	.	.	0.30	0.67
Ala	107	A	A	.	.	.	.	.	0.01	0.06	.	.	.	-0.30	0.39
Val	108	A	A	.	.	.	.	.	-0.80	0.49	.	*	.	-0.60	0.38
Thr	109	A	A	.	.	.	.	.	-0.76	0.67	.	*	.	-0.60	0.20
Ala	110	A	A	.	.	.	.	.	-1.06	0.24	*	*	.	-0.30	0.40
Gly	111	A	A	.	.	.	.	.	-1.54	0.43	*	*	.	-0.60	0.38
Leu	112	A	A	.	.	.	.	.	-0.96	0.57	.	*	.	-0.60	0.23
Lys	113	.	A	B	.	.	.	.	-0.31	0.09	.	*	*	-0.30	0.39
Ile	114	.	A	B	.	.	.	.	-0.21	0.01	.	*	.	-0.30	0.61
Phe	115	.	A	B	.	.	.	.	-0.21	0.01	.	*	.	0.15	1.15
Glu	116	.	A	.	.	.	.	C	-0.08	-0.17	.	*	F	1.25	0.58
Pro	117	.	A	.	.	.	.	C	0.39	0.26	.	*	F	1.10	1.28
Pro	118	.	.	.	.	.	.	C	0.34	-0.00	.	.	F	2.20	1.47
Ala	119	.	.	.	.	.	T	C	0.89	-0.79	.	*	F	3.00	1.47
Pro	120	.	.	.	.	.	T	C	1.59	-0.36	.	*	F	2.25	0.94
Gly	121	.	.	.	.	T	T	.	1.29	-0.39	.	*	F	2.15	0.98
Glu	122	.	.	.	.	T	T	.	1.20	-0.43	.	.	F	2.00	1.30
Gly	123	.	.	.	.	.	.	C	1.41	-0.54	.	.	F	1.60	1.12
Asn	124	.	.	.	.	.	.	C	2.00	-0.57	.	.	F	1.50	1.97
Ser	125	.	.	.	.	.	.	C	1.91	-0.60	.	*	F	1.50	1.82
Ser	126	.	.	.	.	.	T	C	2.37	-0.21	.	*	F	1.54	2.47
Gln	127	.	.	.	.	.	T	C	2.37	-0.64	.	*	F	2.18	3.01
Asn	128	.	.	.	.	.	.	C	2.76	-0.64	.	.	F	2.32	3.61
Ser	129	.	.	.	.	.	T	C	2.87	-1.03	.	.	F	2.86	5.39
Arg	130	.	.	.	.	T	.	.	2.58	-1.41	*	.	F	3.40	6.09
Asn	131	.	.	.	.	T	T	.	2.02	-1.31	*	.	F	3.06	3.83
Lys	132	.	.	.	.	T	T	.	2.02	-1.07	*	.	F	2.72	2.12
Arg	133	.	.	.	.	T	.	.	1.68	-1.06	*	.	F	2.18	1.88
Ala	134	.	.	.	.	.	.	C	1.77	-0.63	*	.	F	1.64	1.15
Val	135	.	.	.	.	.	.	C	1.66	-0.60	*	.	F	1.49	0.89
Gln	136	.	.	.	.	.	.	C	1.66	-0.60	*	.	F	1.83	0.79
Gly	137	.	.	.	.	.	T	C	1.50	-0.60	*	.	F	2.52	1.35
Pro	138	.	.	.	.	.	T	C	0.33	-0.61	*	.	F	2.86	2.63
Glu	139	.	.	.	.	T	T	.	0.61	-0.61	*	.	F	3.40	1.13
Glu	140	A	.	.	.	.	T	.	1.47	-0.53	.	*	F	2.66	1.64
Thr	141	A	.	.	.	.	.	.	1.47	-0.56	.	.	F	2.12	1.84
Val	142	A	.	.	.	.	.	.	1.14	-0.99	.	.	F	1.78	1.77
Thr	143	A	.	.	.	.	T	.	0.54	-0.41	.	.	F	1.19	0.55
Gln	144	A	.	.	.	.	T	.	0.54	0.27	*	.	F	0.25	0.31
Asp	145	A	.	.	.	.	T	.	-0.27	0.19	*	.	F	0.25	0.73
Cys	146	A	.	.	.	.	T	.	-0.84	0.23	*	.	.	0.10	0.42
Leu	147	A	A	.	.	.	.	.	-0.58	0.43	*	.	.	-0.60	0.17
Gln	148	A	A	.	.	.	.	.	-0.27	0.53	*	.	.	-0.60	0.10
Leu	149	A	A	.	.	.	.	.	-0.57	0.53	*	.	.	-0.30	0.32
Ile	150	A	A	.	.	.	.	.	-0.57	0.34	*	.	.	0.30	0.52
Ala	151	.	A	.	.	.	.	C	-0.21	-0.34	.	*	.	1.40	0.52
Asp	152	.	.	.	.	T	T	.	0.39	-0.26	.	*	F	2.45	0.91
Ser	153	.	.	.	.	.	.	C	0.08	-0.51	.	.	F	3.00	2.00
Glu	154	.	.	.	.	.	.	C	-0.00	-0.71	.	.	F	2.70	2.86
Thr	155	.	.	.	.	.	T	C	0.89	-0.53	*	.	F	2.40	1.20
Pro	156	.	.	.	B	.	.	C	1.52	-0.13	*	.	F	1.56	1.55
Thr	157	.	.	.	B	T	.	.	1.18	-0.51	*	.	F	1.92	1.79
Ile	158	A	.	.	B	.	.	.	1.18	-0.09	.	.	F	1.08	1.23
Gln	159	.	.	.	.	.	T	.	0.93	-0.19	.	.	F	2.04	1.07
Lys	160	.	.	.	.	.	T	.	0.93	0.14	*	.	F	1.60	1.16
Gly	161	.	.	.	.	T	T	.	0.44	0.14	*	.	F	1.44	2.38
Ser	162	.	.	.	.	T	T	.	-0.10	0.24	*	.	F	1.28	1.19
Tyr	163	.	.	.	B	T	.	.	0.58	0.49	*	.	.	0.12	0.44
Thr	164	.	.	B	B	.	.	.	0.29	0.91	*	.	.	-0.44	0.69
Phe	165	.	.	B	B	.	.	.	-0.57	1.40	*	.	.	-0.60	0.54
Val	166	.	.	B	B	.	.	.	-1.03	1.70	.	.	.	-0.60	0.29
Pro	167	.	.	B	B	.	.	.	-1.03	1.63	.	.	.	-0.60	0.16
Trp	168	A	.	B	.	.	.	.	-1.49	1.53	.	*	.	-0.60	0.25
Leu	169	A	.	B	.	.	.	.	-1.13	1.53	*	.	.	-0.60	0.29
Leu	170	A	.	B	.	.	.	.	-0.32	0.89	.	.	.	-0.30	0.38
Ter	171	A	.	.	.	.	.	.	0.19	0.46	*	.	.	0.20	0.71
Phe	172	.	.	.	.	T	.	.	0.10	-0.03	*	.	.	1.80	0.85
Lys	173	.	.	.	.	T	T	.	-0.20	-0.33	.	.	F	2.60	1.38
Arg	174	.	.	.	.	T	T	C	-0.20	-0.51	.	.	F	3.00	1.04

TABLE 9-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	
Gly	175	.	.	.	.	.	T	C	0.61	-0.21	.	.	F	2.25	0.99	
Ser	176	A	.	.	.	.	T	.	0.91	-1.00	*	.	F	2.05	0.86	
Ala	177	A	A	.	.	.	.	.	1.66	-1.00	*	.	F	1.35	0.76	
Leu	178	A	A	.	.	.	.	.	1.61	-1.00	*	.	F	1.20	1.54	
Glu	179	A	A	.	.	.	.	.	1.50	-1.43	.	.	F	0.90	1.98	
Glu	180	A	A	.	.	.	.	.	1.89	-1.41	*	.	F	0.90	3.16	
Lys	181	A	A	.	.	.	.	.	1.30	-1.91	*	.	F	0.90	7.66	
Glu	182	A	A	.	.	.	.	.	1.08	-1.91	.	.	F	0.90	3.10	
Asn	183	A	A	.	.	.	.	.	1.03	-1.23	*	.	F	0.90	1.48	
Lys	184	A	A	.	.	.	.	.	1.08	-0.59	*	.	F	0.75	0.55	
Ile	185	A	A	.	.	.	.	.	1.08	-0.59	*	.	.	0.60	0.63	
Leu	186	A	A	.	.	.	.	.	0.72	-0.59	*	.	.	0.60	0.68	
Val	187	A	A	.	.	.	.	.	0.38	-0.50	.	.	.	0.30	0.49	
Lys	188	A	A	.	.	.	.	.	0.13	-0.07	*	.	F	0.45	0.69	
Glu	189	A	.	.	.	.	T	.	-0.61	0.00	.	.	F	0.40	1.32	
Thr	190	.	.	.	.	.	T	.	-0.42	0.10	.	.	F	0.80	1.54	
Gly	191	.	.	.	.	.	T	T	-0.50	0.24	*	.	F	0.65	0.67	
Tyr	192	.	.	.	.	.	T	T	0.11	0.93	*	.	.	0.20	0.27	
Phe	193	.	.	B	B	.	.	.	-0.28	1.69	.	.	.	-0.60	0.29	
Phe	194	.	.	B	B	.	.	.	-0.28	1.63	.	.	.	-0.60	0.29	
Ile	195	.	.	B	B	.	.	.	-0.82	1.60	.	.	.	-0.60	0.32	
Tyr	196	.	.	B	B	.	.	.	-1.29	1.49	.	.	.	-0.60	0.28	
Gly	197	.	.	.	B	T	.	.	-1.29	1.39	.	.	.	-0.20	0.26	
Gln	198	.	.	.	B	T	.	.	-0.90	1.36	.	.	.	-0.20	0.59	
Val	199	.	.	.	B	.	.	C	-0.20	1.16	.	.	.	-0.40	0.54	
Leu	200	.	.	.	B	.	.	.	C	0.73	0.40	.	.	-0.10	0.92	
Tyr	201	.	.	.	.	T	.	.	0.67	-0.03	.	.	.	1.25	1.06	
Thr	202	.	.	.	.	T	T	.	0.77	0.06	.	.	F	0.80	2.06	
Asp	203	.	.	.	.	T	T	.	0.18	0.17	.	.	F	0.80	3.91	
Lys	204	A	.	.	.	.	.	.	0.43	-0.01	.	.	F	1.00	2.52	
Thr	205	A	A	.	.	.	.	.	0.90	-0.16	.	.	F	0.60	1.73	
Tyr	206	A	A	.	.	.	.	.	1.11	-0.21	.	.	.	0.45	1.03	
Ala	207	A	A	.	.	.	.	.	0.61	0.29	.	.	.	-0.30	0.70	
Met	208	A	A	.	.	.	.	.	-0.28	0.97	.	.	.	-0.60	0.40	
Gly	209	A	A	.	B	.	.	.	-0.32	1.17	*	.	.	-0.60	0.18	
His	210	A	A	.	B	.	.	.	0.10	0.81	*	.	.	-0.60	0.31	
Leu	211	A	A	.	B	.	.	.	0.39	0.31	.	.	.	-0.30	0.61	
Ile	212	A	A	.	B	.	.	.	1.02	-0.30	.	.	.	0.45	1.22	
Gln	213	A	A	.	B	.	.	.	0.77	-0.73	*	.	.	0.75	1.80	
Arg	214	A	A	.	B	.	.	.	1.08	-0.59	*	.	F	0.90	1.62	
Lys	215	A	A	.	B	.	.	.	0.26	-0.77	*	.	F	0.90	3.14	
Lys	216	A	A	.	B	.	.	.	0.37	-0.81	*	.	F	0.90	1.35	
Val	217	.	A	B	B	.	.	.	0.91	-0.43	*	.	.	0.30	0.60	
His	218	.	A	B	B	.	.	.	0.91	-0.00	.	.	.	0.30	0.29	
Val	219	.	A	B	B	.	.	.	0.80	-0.00	*	.	.	0.30	0.25	
Phe	220	.	.	B	B	.	.	.	-0.06	-0.00	*	.	.	0.30	0.57	
Gly	221	A	.	.	B	.	.	.	-0.40	0.04	.	.	.	-0.30	0.35	
Asp	222	A	.	.	.	.	.	.	-0.36	-0.07	*	.	.	0.50	0.63	
Glu	223	A	.	.	.	.	.	.	-1.18	-0.03	.	.	.	0.50	0.60	
Leu	224	A	.	.	B	.	.	.	-0.63	-0.17	.	.	.	0.30	0.45	
Ser	225	A	.	.	.	B	.	.	-0.74	-0.11	.	.	.	0.30	0.39	
Leu	226	A	.	.	B	.	.	.	-1.10	0.57	.	.	.	-0.60	0.18	
Val	227	A	.	.	B	.	.	.	-0.99	1.36	.	.	.	-0.60	0.19	
Thr	228	A	.	.	B	.	.	.	-1.66	0.67	*	.	.	-0.60	0.28	
Leu	229	A	.	.	B	.	.	.	-1.73	0.86	*	.	.	-0.60	0.18	
Phe	230	A	.	.	B	.	.	.	-1.43	0.86	*	.	.	-0.60	0.17	
Arg	231	A	.	.	B	.	.	.	-0.62	0.61	*	.	.	-0.60	0.21	
Cys	232	.	.	.	B	T	.	.	-0.37	0.53	*	.	.	-0.20	0.41	
Ile	233	.	.	.	B	T	.	.	-0.27	0.46	*	.	.	-0.20	0.46	
Gln	234	.	.	.	B	T	.	.	0.54	0.10	*	.	.	0.10	0.37	
Asn	235	.	.	.	B	.	.	C	0.93	0.10	.	.	.	0.05	1.19	
Met	236	.	.	.	B	.	.	.	C	0.01	0.01	.	.	F	0.20	2.44
Pro	237	.	.	.	B	.	.	.	C	0.47	0.01	*	.	F	0.44	1.16
Glu	238	.	.	.	.	T	.	.	1.36	0.04	*	.	F	1.08	1.12	
Thr	239	.	.	.	.	.	.	C	1.36	0.04	*	.	F	1.12	1.82	
Leu	240	.	.	.	.	.	.	.	C	1.06	-0.17	*	.	F	1.96	1.89
Pro	241	.	.	.	.	T	.	.	0.99	-0.21	.	.	F	2.40	1.46	
Asn	242	.	.	.	.	T	.	.	0.96	0.36	.	.	F	1.41	0.54	
Asn	243	.	.	.	.	T	T	.	0.66	0.63	.	.	F	1.22	1.03	
Ser	244	.	.	.	.	T	T	.	0.38	0.33	.	.	F	1.13	0.89	
Cys	245	.	.	.	.	T	T	.	0.84	0.40	.	.	.	0.74	0.56	
Tyr	246	.	.	.	.	T	T	.	0.17	0.43	.	.	.	0.20	0.35	
Ser	247	A	.	.	.	.	.	.	-0.42	0.71	.	.	.	-0.40	0.18	
Ala	248	A	A	.	.	.	.	.	-0.38	0.83	.	.	.	-0.60	0.34	
Gly	249	A	A	.	.	.	.	.	-0.89	0.26	.	.	.	-0.30	0.43	
Ile	250	A	A	.	.	.	.	.	-0.22	0.19	*	.	.	-0.30	0.27	
Ala	251	A	.	.	.	.	.	.	0.02	-0.20	*	.	.	0.30	0.46	

TABLE 9-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Lys	252	A	A	.	.	.	.	.	-0.02	-0.70	.	.	.	0.60	0.80
Leu	253	A	A	.	.	.	.	.	0.57	-0.70	.	.	.	F	0.90 1.13
Glu	254	A	A	.	.	.	.	.	0.91	-1.39	.	.	F	0.90	1.87
Glu	255	A	A	.	.	.	.	.	0.99	-1.89	.	.	F	0.90	1.62
Gly	256	A	A	.	.	.	.	.	1.58	-1.20	.	.	F	0.90	1.62
Asp	257	A	A	.	.	.	.	.	0.72	-1.49	.	.	F	0.90	1.62
Glu	258	A	A	.	.	.	.	.	0.94	-0.80	.	.	F	0.75	0.77
Leu	259	A	A	.	.	.	.	.	0.06	-0.30	.	.	.	0.30	0.79
Glu	260	A	A	.	.	.	.	.	-0.16	-0.04	.	.	.	0.30	0.33
Leu	261	A	A	.	.	.	.	.	0.30	0.39	.	.	.	-0.30	0.30
Ala	262	A	A	.	.	.	.	.	0.30	0.39	.	.	.	-0.30	0.70
Ile	263	A	A	.	.	.	.	.	0.30	-0.30	.	.	.	0.30	0.70
Pro	264	A	.	.	.	.	T	.	0.52	-0.30	.	.	F	1.00	1.37
Arg	265	A	.	.	.	.	T	.	0.52	-0.49	.	.	F	1.00	1.37
Glu	266	A	.	.	.	.	T	.	0.44	-0.59	.	.	F	1.30	3.38
Asn	267	A	.	.	.	.	T	.	0.73	-0.59	.	.	F	1.30	1.53
Ala	268	A	.	.	.	.	.	.	0.81	-0.63	.	.	.	0.95	1.05
Glu	269	A	.	.	.	.	.	.	1.02	0.06	.	.	.	-0.10	0.50
Ile	270	A	.	.	.	.	.	.	0.57	0.06	.	.	.	0.15	0.52
Ser	271	.	.	.	.	.	C	.	0.57	0.09	.	.	.	0.60	0.51
Leu	272	.	.	.	.	.	C	.	-0.29	-0.41	.	.	F	1.60	0.49
Asp	273	.	.	.	.	.	T	.	-0.01	-0.17	.	.	F	2.25	0.52
Gly	274	.	.	.	.	T	T	.	-0.71	-0.37	.	.	F	2.50	0.56
Asp	275	.	.	.	.	T	T	.	-0.52	0.03	.	.	F	1.65	0.59
Val	276	A	.	.	.	.	T	.	-0.57	0.13	.	.	F	1.00	0.30
Thr	277	A	.	.	B	.	.	.	-0.34	0.56	.	.	.	-0.10	0.30
Phe	278	A	.	.	B	.	.	.	-1.16	0.63	.	.	.	-0.35	0.18
Phe	279	A	.	.	B	.	.	.	-0.77	1.31	.	.	.	-0.60	0.20
Gly	280	A	A	.	.	.	.	.	-1.58	0.67	.	.	.	-0.60	0.28
Ala	281	A	A	.	.	.	.	.	-1.53	0.87	.	.	.	-0.60	0.27
Leu	282	A	A	.	.	.	.	.	1.61	0.77	.	.	.	-0.60	0.26
Lys	283	A	A	.	.	.	.	.	-1.30	0.41	.	.	.	-0.60	0.33
Leu	284	A	A	.	.	.	.	.	-0.99	0.41	.	.	.	-0.60	0.42
Leu	285	A	A	.	.	.	.	.	-1.03	0.34	.	.	.	-0.30	0.65

TABLE 10

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	.	.	.	.	.	.	0.73	-0.71	.	.	.	0.95	1.39
Asp	2	A	.	.	.	.	T	.	1.12	-0.66	.	.	.	1.15	1.56
Asp	3	A	.	.	.	.	T	.	1.62	-1.09	.	.	.	1.15	2.12
Ser	4	A	.	.	.	.	.	.	2.01	-1.51	.	.	.	1.15	4.19
Thr	5	A	.	.	.	.	T	.	2.40	-2.13	.	.	F	1.30	4.35
Glu	6	A	A	.	.	.	.	.	2.70	-1.73	.	.	F	0.90	4.51
Arg	7	A	A	.	.	.	.	.	2.81	-1.34	.	.	F	0.90	4.51
Glu	8	A	A	.	.	.	.	.	2.00	-1.73	.	.	F	0.90	6.12
Glu	9	A	A	.	.	.	.	.	1.99	-1.53	.	.	F	0.90	2.91
Ser	10	A	.	.	B	.	.	.	2.00	-1.04	.	.	F	0.90	2.15
Arg	11	A	.	.	B	.	.	.	1.33	-0.66	.	.	F	0.90	1.66
Leu	12	A	.	.	B	.	.	.	0.41	-0.09	.	.	F	0.45	0.51
Thr	13	A	.	.	B	.	.	.	0.46	0.20	.	.	F	-0.15	0.32
Ser	14	A	A	.	.	.	.	.	0.50	-0.19	.	.	.	0.30	0.32
Cys	15	A	A	.	.	.	.	.	0.91	-0.19	.	.	.	0.30	0.78
Leu	16	A	A	.	.	.	.	.	0.80	-0.87	.	.	F	0.90	1.06
Lys	17	A	A	.	.	.	.	.	1.61	-1.36	.	.	F	0.90	1.37
Lys	18	A	A	.	.	.	.	.	1.32	-1.74	.	.	F	0.90	4.44
Arg	19	A	A	.	.	.	.	.	1.67	-1.70	.	.	F	0.90	5.33
Glu	20	A	A	.	.	.	.	.	1.52	-2.39	.	.	F	0.90	5.33
Glu	21	A	A	.	.	.	.	.	2.38	-1.70	.	.	F	0.90	2.20
Met	22	A	A	.	.	.	.	.	2.33	-1.70	.	.	F	0.90	2.24
Lys	23	A	A	.	.	.	.	.	1.62	-1.70	.	.	F	0.90	2.24
Leu	24	A	A	.	.	.	.	.	0.66	-1.13	.	.	F	0.75	0.69
Lys	25	A	A	.	.	.	.	.	0.36	-0.49	.	.	F	0.45	0.52
Glu	26	A	.	B	.	.	.	.	-0.53	-0.71	.	.	.	0.60	0.35
Cys	27	A	.	B	.	.	.	.	-0.74	-0.03	.	.	.	0.30	0.30
Val	28	A	A	.	B	.	.	.	-1.00	-0.03	.	.	.	0.30	0.12
Ser	29	A	A	.	B	.	.	.	-0.08	0.40	.	.	.	-0.30	0.11
Ile	30	A	.	.	B	.	.	.	-0.08	0.40	.	.	.	-0.30	0.40
Leu	31	A	.	.	B	.	.	.	-0.08	-0.17	.	.	.	0.45	1.08
Pro	32	.	.	.	.	.	C	.	0.29	-0.81	.	.	F	1.10	1.39
Arg	33	.	.	.	.	T	.	.	0.93	-0.81	.	.	F	1.50	2.66
Lys	34	.	.	.	.	T	.	.	0.93	-1.07	.	.	F	1.84	4.98
Glu	35	.	.	.	.	.	C	.	0.97	-1.37	.	.	F	1.98	4.32



TABLE 10-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ser	36	.	.	.	.	.	T	C	1.89	-1.16	▪	▪	F	2.52	1.64
Pro	37	.	.	.	.	.	T	C	1.80	-1.16	▪	▪	F	2.86	1.60
Ser	38	.	.	.	.	T	T	.	1.39	-0.77	▪	.	F	3.40	1.24
Val	39	A	.	.	.	.	T	.	1.39	-0.39	▪	.	F	2.36	1.24
Arg	40	A	.	.	.	.	.	.	1.39	-0.77	▪	.	F	2.46	1.60
Ser	41	A	.	.	.	.	.	.	1.34	-1.20	▪	▪	F	2.46	2.00
Ser	42	.	.	.	.	T	T	.	1.60	-1.16	▪	.	F	3.06	2.67
Lys	43	.	.	.	.	T	T	.	1.09	-1.80	▪	▪	F	3.06	2.72
Asp	44	.	.	.	.	T	T	.	1.13	-1.11	▪	▪	F	3.40	1.67
Gly	45	A	.	.	.	.	T	.	0.43	-0.81	▪	▪	F	2.66	1.03
Lys	46	A	A	.	.	.	.	.	0.14	-0.70	▪	.	F	1.77	0.52
Leu	47	A	A	.	.	.	.	.	0.13	-0.20	▪	.	.	0.98	0.31
Leu	48	A	A	.	.	.	.	.	-0.72	0.29	▪	.	.	0.04	0.46
Ala	49	A	A	.	.	.	.	.	-1.53	0.54	▪	.	.	-0.60	0.19
Ala	50	A	A	.	.	.	.	.	-2.00	1.23	.	.	.	-0.60	0.19
Thr	51	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.19
Leu	52	A	A	.	.	.	.	.	-2.63	1.04	.	.	.	-0.60	0.19
Leu	53	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.15
Leu	54	A	A	.	.	.	.	.	-2.34	1.41	.	.	.	-0.60	0.09
Ala	55	A	A	.	.	.	.	.	-2.42	1.31	.	.	.	-0.60	0.14
Leu	56	A	A	.	.	.	.	.	-2.78	1.20	.	.	.	-0.60	0.09
Leu	57	A	.	.	.	.	.	.	-2.78	1.09	.	.	.	-0.20	0.06
Ser	58	A	.	.	.	T	.	.	-2.28	1.09	.	.	.	-0.20	0.05
Cys	59	A	.	.	.	T	.	.	-2.32	1.07	.	.	.	-0.20	0.09
Cys	60	A	.	.	.	T	.	.	-2.59	1.03	.	.	.	-0.20	0.08
Leu	61	.	B	B	.	.	.	.	-2.08	0.99	.	.	.	-0.60	0.04
Thr	62	.	B	B	.	.	.	.	-1.97	0.99	.	.	.	-0.60	0.11
Val	63	.	B	B	.	.	.	.	-1.91	1.20	.	.	.	-0.60	0.17
Val	64	.	B	B	.	.	.	.	-1.24	1.39	.	.	.	-0.60	0.33
Ser	65	.	B	B	.	.	.	.	-1.43	1.10	.	.	.	-0.60	0.40
Phe	66	A	.	B	.	.	.	.	-1.21	1.26	.	.	.	-0.60	0.40
Tyr	67	A	.	B	.	.	.	.	-1.49	1.11	.	.	.	-0.60	0.54
Glu	68	A	.	B	.	.	.	.	-1.44	0.97	.	.	.	-0.60	0.41
Val	69	A	.	B	.	.	.	.	-0.59	1.27	.	.	.	-0.60	0.39
Ala	70	A	.	B	.	.	.	.	-0.63	0.89	.	.	.	-0.60	0.43
Ala	71	A	.	B	.	.	.	.	0.07	0.56	▪	.	.	-0.60	0.25
Leu	72	A	.	.	.	T	.	.	-0.50	0.16	.	.	.	0.10	0.55
Glu	73	A	.	.	.	T	.	.	-1.09	0.20	.	F	.	0.25	0.45
Gly	74	A	.	.	.	T	.	.	-0.53	0.20	.	F	.	0.25	0.45
Asp	75	A	.	.	.	T	.	.	-0.76	0.09	▪	F	.	0.25	0.73
Leu	76	A	A	.	.	.	.	.	-0.06	0.09	▪	F	.	-0.15	0.35
Ala	77	A	A	.	.	.	.	.	0.17	-0.31	▪	.	.	0.30	0.69
Ser	78	A	A	.	.	.	.	.	0.17	-0.24	▪	.	.	0.30	0.42
Leu	79	A	A	.	.	.	.	.	-0.30	-0.24	▪	.	.	0.30	0.88
Arg	80	A	A	.	.	.	.	.	-0.30	-0.24	▪	.	.	0.30	0.72
Ala	81	A	A	.	.	.	.	.	0.17	-0.34	▪	.	.	0.30	0.93
Glu	82	A	A	.	.	.	.	.	0.72	-0.30	▪	.	.	0.45	1.11
Leu	83	A	A	.	.	.	.	.	0.99	-0.49	▪	.	.	0.30	0.77
Glu	84	A	A	.	.	.	.	.	1.21	0.01	▪	.	.	-0.15	1.04
Gly	85	A	A	.	.	.	.	.	1.10	0.01	▪	.	.	-0.30	0.61
His	86	A	A	.	.	.	.	.	1.73	0.01	▪	.	.	-0.15	1.27
His	87	A	A	.	.	.	.	.	0.92	-0.67	▪	.	.	0.75	1.47
Ala	88	A	A	.	.	.	.	.	1.52	-0.39	▪	.	.	0.45	1.22
Glu	89	A	A	.	.	.	.	.	0.93	-0.39	▪	.	.	0.45	1.39
Lys	90	A	A	.	.	.	.	.	0.93	-0.39	▪	F	.	0.60	1.03
Leu	91	A	.	.	.	T	.	.	0.38	-0.46	▪	.	.	0.85	1.01
Pro	92	A	.	.	.	T	.	.	0.07	-0.46	▪	.	.	0.70	0.59
Ala	93	A	.	.	.	T	.	.	0.07	-0.03	▪	.	.	0.70	0.29
Gly	94	A	.	.	.	T	.	.	-0.14	0.47	▪	.	.	-0.20	0.36
Ala	95	A	.	.	.	.	.	.	-0.14	0.21	▪	.	.	-0.10	0.36
Gly	96	A	.	.	.	.	.	.	0.08	-0.21	.	F	.	0.65	0.71
Ala	97	A	.	.	.	.	.	.	-0.06	-0.21	.	F	.	0.65	0.72
Pro	98	A	.	.	.	.	.	.	-0.28	-0.21	▪	F	.	0.65	0.71
Lys	99	A	A	.	.	.	.	.	0.07	-0.03	.	F	.	0.45	0.59
Ala	100	A	A	.	.	.	.	.	0.66	-0.46	.	F	.	0.60	1.01
Gly	101	A	A	.	.	.	.	.	0.41	-0.96	.	F	.	0.90	1.13
Leu	102	A	A	.	.	.	.	.	0.79	-0.89	.	F	.	0.75	0.57
Glu	103	A	A	.	.	.	.	.	0.41	-0.46	.	F	.	0.45	0.88
Glu	104	A	A	.	.	.	.	.	-0.49	-0.46	▪	F	.	0.45	0.89
Ala	105	A	A	.	.	.	.	.	-0.21	-0.24	.	.	.	0.30	0.81
Pro	106	A	A	.	.	.	.	.	-0.46	-0.44	.	.	.	0.30	0.67
Ala	107	A	A	.	.	.	.	.	0.01	0.06	.	.	.	-0.30	0.39
Val	108	A	A	.	.	.	.	.	-0.80	0.49	▪	.	.	-0.60	0.38
Thr	109	A	A	.	.	.	.	.	-0.76	0.67	▪	.	.	-0.60	0.20
Ala	110	A	A	.	.	.	.	.	-1.06	0.24	▪	.	.	-0.30	0.40
Gly	111	A	A	.	.	.	.	.	-1.54	0.43	▪	.	.	-0.60	0.38
Leu	112	A	A	.	.	.	.	.	-0.96	0.57	▪	.	.	-0.60	0.23

TABLE 10-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Lys	113	-	A	B	-	-	-	-	-0.31	0.09	*	*	-	-0.30	0.39
Ile	114	-	A	B	-	-	-	-	-0.21	0.01	*	-	-	-0.30	0.61
Phe	115	-	A	B	-	-	-	-	-0.21	0.01	*	-	-	0.15	1.15
Glu	116	-	A	-	-	-	-	C	-0.08	-0.17	*	-	F	1.25	0.58
Pro	117	-	A	-	-	-	-	C	0.39	0.26	*	-	F	1.10	1.28
Pro	118	-	-	-	-	-	-	C	0.34	0.00	*	-	F	2.20	1.47
Ala	119	-	-	-	-	-	-	T	0.89	-0.79	*	-	F	3.00	1.47
Pro	120	-	-	-	-	-	-	T	1.59	-0.36	*	-	F	2.25	0.94
Gly	121	-	-	-	T	T	-	-	1.29	-0.39	*	-	F	2.15	0.98
Glu	122	-	-	-	T	T	-	-	1.20	-0.43	*	-	F	2.00	1.30
Gly	123	-	-	-	-	-	-	C	1.41	-0.54	*	-	F	1.60	1.12
Asn	124	-	-	-	-	-	-	T	2.00	-0.57	*	-	F	1.50	1.97
Ser	125	-	-	-	-	-	-	T	1.91	-0.60	*	-	F	1.50	1.82
Ser	126	-	-	-	-	-	-	T	2.37	-0.21	*	-	F	1.54	2.47
Gln	127	-	-	-	-	-	-	T	2.37	-0.64	*	-	F	2.18	3.01
Asn	128	-	-	-	-	-	-	C	2.76	-0.64	*	-	F	2.32	3.61
Ser	129	-	-	-	-	-	-	T	2.87	-1.03	*	-	F	2.86	5.39
Arg	130	-	-	-	-	-	-	T	2.58	-1.41	*	-	F	3.40	6.09
Asn	131	-	-	-	-	-	-	T	2.02	-1.31	*	-	F	3.06	3.83
Lys	132	-	-	-	-	-	-	T	2.02	-1.07	*	-	F	2.72	2.12
Arg	133	-	-	-	-	-	-	T	1.68	-1.06	*	-	F	2.18	1.88
Ala	134	-	-	-	-	-	-	C	1.77	-0.63	*	-	F	1.64	1.15
Val	135	-	-	-	-	-	-	C	1.66	-0.60	*	-	F	1.15	0.89
Gln	136	-	-	-	-	-	-	C	1.66	-0.60	*	-	F	1.49	0.79
Gly	137	-	-	-	-	-	-	C	1.30	-0.60	*	-	F	2.18	1.35
Pro	138	-	-	-	-	-	-	T	0.84	-0.61	*	-	F	2.52	2.63
Glu	139	-	-	-	-	-	-	T	1.13	-0.83	*	-	F	2.86	1.50
Glu	140	-	-	-	-	-	-	T	1.74	-0.84	*	-	F	3.40	2.03
Thr	141	-	-	-	-	-	-	T	1.43	-0.51	*	-	F	2.86	2.06
Gly	142	-	-	-	-	-	-	T	1.08	-0.46	*	-	F	2.42	1.72
Ser	143	-	-	-	-	-	-	T	0.43	0.33	*	-	F	1.33	0.86
Tyr	144	-	-	-	-	-	-	T	0.22	0.97	*	-	F	0.54	0.44
Thr	145	-	-	-	-	-	-	T	-0.07	0.91	*	-	-	0.20	0.69
Phe	146	-	-	B	B	-	-	-	-0.57	1.40	*	-	-	-0.60	0.54
Val	147	-	-	B	B	-	-	-	-1.03	1.70	*	-	-	-0.60	0.29
Pro	148	-	-	B	B	-	-	-	-1.03	1.63	*	-	-	-0.60	0.16
Trp	149	A	-	-	-	-	-	-	-1.49	1.53	*	-	-	-0.60	0.25
Leu	150	A	-	B	-	-	-	-	-1.13	1.53	*	-	-	-0.60	0.29
Leu	151	A	-	B	-	-	-	-	-0.32	0.89	*	-	-	-0.30	0.38
Ser	152	A	-	-	-	-	-	-	0.19	0.46	*	-	-	0.20	0.71
Phe	153	-	-	-	-	-	-	T	0.10	-0.03	*	-	-	1.80	0.85
Lys	154	-	-	-	-	-	-	T	-0.20	-0.33	*	-	F	2.60	1.38
Arg	155	-	-	-	-	-	-	T	-0.20	-0.51	*	-	F	3.00	1.94
Gly	156	-	-	-	-	-	-	T	0.61	-0.21	*	-	F	2.25	0.99
Ser	157	A	-	-	-	-	-	T	0.91	-1.00	*	-	F	2.05	0.86
Ala	158	A	A	-	-	-	-	-	1.66	-1.00	*	-	F	1.35	0.76
Leu	159	A	A	-	-	-	-	-	1.61	-1.00	*	-	F	1.20	1.54
Glu	160	A	A	-	-	-	-	-	1.50	-1.43	*	-	F	0.90	1.98
Glu	161	A	A	-	-	-	-	-	1.89	-1.41	*	-	F	0.90	3.16
Lys	162	A	A	-	-	-	-	-	1.30	-1.91	*	-	F	0.90	7.66
Glu	163	A	A	-	-	-	-	-	1.08	-1.91	*	-	F	0.90	3.10
Asn	164	A	A	-	-	-	-	-	1.03	-1.23	*	-	F	0.90	1.48
Lys	165	A	A	-	-	-	-	-	1.08	-0.59	*	-	F	0.75	0.55
Ile	166	A	A	-	-	-	-	-	1.08	-0.59	*	-	-	0.60	0.63
Leu	167	A	A	-	-	-	-	-	0.72	-0.59	*	-	-	0.76	0.88
Val	168	A	A	-	-	-	-	-	0.38	-0.50	*	-	-	0.92	0.49
Lys	169	A	A	-	-	-	-	-	0.13	-0.07	*	-	F	0.93	0.69
Glu	170	A	-	-	-	-	-	T	-0.61	0.00	*	-	F	1.64	1.32
Thr	171	-	-	-	-	-	-	T	-0.42	0.10	*	-	F	1.60	1.54
Gly	172	-	-	-	-	-	-	T	-0.50	0.24	*	-	F	1.29	0.67
Tyr	173	-	-	-	-	-	-	T	0.11	0.93	*	-	-	0.68	0.27
Phe	174	-	-	B	B	-	-	-	-0.28	1.69	*	-	-	-0.28	0.29
Phe	175	-	-	B	B	-	-	-	-0.28	1.63	*	-	-	-0.44	0.29
Ile	176	-	-	B	B	-	-	-	-0.82	1.60	*	-	-	-0.60	0.32
Tyr	177	-	-	B	B	-	-	-	-1.29	1.49	*	-	-	-0.60	0.28
Gly	178	-	-	B	T	-	-	-	-1.29	1.39	*	-	-	-0.20	0.26
Gln	179	-	-	B	T	-	-	-	-0.90	1.36	*	-	-	-0.20	0.59
Val	180	-	-	B	-	-	-	C	-0.20	1.16	*	-	-	-0.40	0.54
Leu	181	-	-	B	-	-	-	C	0.73	0.40	*	-	-	-0.10	0.92
Tyr	182	-	-	-	-	-	-	T	0.67	-0.03	*	-	-	1.25	1.06
Thr	183	-	-	-	-	-	-	T	0.77	0.06	*	-	-	0.80	2.06
Asp	184	-	-	-	-	-	-	T	0.18	0.17	*	-	F	0.80	3.91
Lys	185	A	-	-	-	-	-	T	0.43	-0.01	*	-	F	1.00	2.52
Thr	186	A	A	-	-	-	-	-	0.90	-0.16	*	-	F	0.60	1.73
Tyr	187	A	A	-	-	-	-	-	1.11	-0.21	*	-	-	0.45	1.03
Ala	188	A	A	-	-	-	-	-	0.61	0.29	*	-	-	-0.30	0.70
Met	189	A	A	-	-	-	-	-	-0.28	0.97	*	-	-	-0.60	0.40

TABLE 10-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Gly	190	A	A	.	B	.	.	.	-0.32	1.17	*	.	.	-0.60	0.18
His	191	A	A	.	B	.	.	.	0.10	0.81	*	.	.	-0.60	0.31
Leu	192	A	A	.	B	.	.	.	0.39	0.31	.	.	.	-0.30	0.61
Ile	193	A	A	.	B	.	.	.	1.02	-0.30	.	.	.	-0.45	1.22
Gln	194	A	A	.	B	.	.	.	0.77	-0.73	.	*	.	0.75	1.80
Arg	195	A	A	.	B	.	.	.	1.08	-0.59	*	*	F	0.90	1.62
Lys	196	A	A	.	B	.	.	.	0.26	-0.77	*	*	F	0.90	1.34
Lys	197	A	A	.	B	.	.	.	0.37	-0.81	.	*	F	0.90	1.35
Val	198	.	A	B	B	.	.	.	0.91	-0.43	*	*	.	0.30	0.60
His	199	.	A	B	B	.	.	.	0.91	0.00	*	*	.	0.30	0.29
Val	200	.	A	B	B	.	.	.	0.80	0.00	*	*	.	0.30	0.25
Phe	201	.	.	B	B	.	.	.	-0.06	0.00	*	.	.	0.30	0.57
Gly	202	A	.	.	B	.	.	.	-0.40	0.04	.	*	.	-0.30	0.35
Asp	203	A	.	.	.	.	.	.	-0.36	-0.07	*	.	.	0.50	0.63
Glu	204	A	.	.	.	.	.	.	-1.18	-0.03	*	.	.	0.50	0.60
Leu	205	A	.	.	B	.	.	.	-0.63	-0.17	.	.	.	0.30	0.45
Ser	206	A	.	.	B	.	.	.	-0.74	-0.11	.	.	.	0.30	0.39
Leu	207	A	.	.	B	.	.	.	-1.10	0.57	.	*	.	-0.60	0.18
Val	208	A	.	.	B	.	.	.	-0.99	1.36	.	*	.	-0.60	0.19
Thr	209	A	.	.	B	.	.	.	-1.66	0.67	*	*	.	-0.60	0.28
Leu	210	A	.	.	B	.	.	.	-1.73	0.86	*	*	.	-0.60	0.18
Phe	211	A	.	.	B	.	.	.	-1.43	0.86	*	*	.	-0.60	0.17
Arg	212	A	.	.	B	.	.	.	-0.62	0.61	*	.	.	-0.60	0.21
Cys	213	.	.	.	B	T	.	.	-0.37	0.53	*	.	.	-0.20	0.41
Ile	214	.	.	.	B	T	.	.	-0.27	0.46	*	.	.	-0.20	0.46
Gln	215	.	.	.	B	T	.	.	0.54	0.10	*	.	.	0.10	0.37
Asn	216	.	.	.	B	.	C	.	0.93	0.10	.	.	.	0.05	1.19
Met	217	.	.	.	B	.	C	.	0.01	0.01	*	.	F	0.20	2.44
Pro	218	.	.	.	B	.	C	.	0.47	0.01	*	.	F	0.44	1.16
Glu	219	.	.	.	.	T	.	C	1.36	0.04	*	.	F	1.08	1.12
Thr	220	.	.	.	.	.	.	C	1.36	0.04	*	.	F	1.12	1.82
Leu	221	.	.	.	.	.	.	C	1.06	-0.17	*	.	F	1.96	1.89
Pro	222	.	.	.	.	T	.	.	0.99	-0.21	.	.	F	2.40	1.46
Asn	223	.	.	.	.	T	.	.	0.96	0.36	.	.	F	1.41	0.54
Asn	224	.	.	.	.	T	T	.	0.66	0.63	.	.	F	1.22	1.03
Ser	225	.	.	.	.	T	T	.	0.38	0.33	.	.	F	1.13	0.89
Cys	226	.	.	.	.	T	T	.	0.84	0.40	.	.	.	0.74	0.56
Tyr	227	.	.	.	.	T	T	.	0.17	0.43	.	.	.	0.20	0.35
Ser	228	A	.	.	.	.	.	.	-0.42	0.71	.	.	.	-0.40	0.18
Ala	229	A	A	.	.	.	.	.	-0.38	0.83	.	.	.	-0.60	0.34
Gly	230	A	A	.	.	.	.	.	-0.89	0.26	.	.	.	-0.30	0.43
Ile	231	A	A	.	.	.	.	.	-0.22	0.19	*	.	.	-0.30	0.27
Ala	232	A	A	.	.	.	.	.	0.02	-0.20	*	.	.	0.30	0.46
Lys	233	A	A	.	.	.	.	.	-0.02	-0.70	.	.	.	0.60	0.80
Leu	234	A	A	.	.	.	.	.	0.57	-0.70	.	F	0.90	1.13	
Glu	235	A	A	.	.	.	.	.	0.91	-1.39	.	F	0.90	1.87	
Glu	236	A	A	.	.	.	.	.	0.99	-1.89	.	F	0.90	1.62	
Gly	237	A	A	.	.	.	.	.	1.58	-1.20	*	F	0.90	1.62	
Asp	238	A	A	.	.	.	.	.	0.72	-1.49	*	F	0.90	1.62	
Glu	239	A	A	.	.	.	.	.	0.94	-0.80	*	F	0.75	0.77	
Leu	240	A	A	.	.	.	.	.	0.06	-0.30	*	.	.	0.30	0.79
Gln	241	A	A	.	.	.	.	.	-0.16	-0.04	*	.	.	0.30	0.33
Leu	242	A	A	.	.	.	.	.	0.30	0.39	*	.	.	-0.30	0.30
Ala	243	A	A	.	.	.	.	.	0.30	0.39	*	.	.	-0.30	0.70
Ile	244	A	A	.	.	.	.	.	0.30	-0.30	*	.	.	0.30	0.70
Pro	245	A	.	.	.	T	.	.	0.52	-0.30	.	F	1.00	1.37	
Arg	246	A	.	.	.	T	.	.	0.52	-0.49	.	F	1.00	1.37	
Glu	247	A	.	.	.	T	.	.	0.44	-0.59	*	F	1.30	3.38	
Asn	248	A	.	.	.	T	.	.	0.73	-0.59	*	F	1.30	1.53	
Ala	249	A	.	.	.	.	.	.	0.81	-0.63	*	.	.	0.95	1.05
Gln	250	A	.	.	.	.	.	.	1.02	0.06	*	.	.	-0.10	0.50
Ile	251	A	.	.	.	.	.	.	0.57	0.06	*	.	.	-0.15	0.52
Ser	252	.	.	.	.	.	C	.	0.57	0.09	.	*	.	0.60	0.51
Leu	253	.	.	.	.	.	C	.	-0.29	-0.41	.	F	1.60	0.49	
Asp	254	.	.	.	.	T	T	.	-0.01	-0.17	.	F	2.25	0.52	
Gly	255	.	.	.	.	T	T	.	-0.71	-0.37	.	F	2.50	0.56	
Asp	256	.	.	.	.	T	T	.	-0.52	0.03	.	F	1.65	0.59	
Val	257	A	.	.	.	.	T	.	-0.57	0.13	.	F	1.00	0.30	
Thr	258	A	.	.	B	.	.	.	-0.34	0.56	.	.	.	-0.10	0.30
Phe	259	A	.	.	B	.	.	.	-1.16	0.63	.	.	.	-0.35	0.18
Phe	260	A	.	.	B	.	.	.	-0.77	1.31	.	.	.	-0.60	0.20
Gly	261	A	A	.	.	.	.	.	-1.58	0.67	*	.	.	-0.60	0.28
Ala	262	A	A	.	.	.	.	.	-1.53	0.87	*	.	.	-0.60	0.27
Leu	263	A	A	.	.	.	.	.	-1.61	0.77	*	.	.	-0.60	0.26
Lys	264	A	A	.	.	.	.	.	-1.30	0.41	*	.	.	-0.60	0.33

TABLE 10-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Leu	265	A	A	.	.	.	.	.	-0.99	0.41	.	.	.	-0.60	0.42
Leu	266	A	A	.	.	.	.	.	-1.03	0.34	.	.	.	-0.30	0.65

In another embodiment, the invention provides antibodies that bind a polypeptide comprising, or alternatively consisting of, an epitope-bearing portion of a polypeptide of the invention. The epitope of this polypeptide portion may be an immunogenic or antigenic epitope of a polypeptide of the invention. An "immunogenic epitope" is defined as a part of a protein that elicits an antibody response when the whole protein is the immunogen. On the other hand, a region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." The number of immunogenic epitopes of a protein generally is less than the number of antigenic epitopes. See, for instance, Geysen et al., *Proc. Natl. Acad. Sci. USA* 81:3998-4002 (1983).

As to the selection of polypeptides bearing an antigenic epitope (i.e., that contain a region of a protein molecule to which an antibody can bind), it is well known in that art that relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for instance, Sutcliffe, J. G., Shinnick, T. M., Green, N. and Learner, R. A. (1983) "Antibodies that react with predetermined sites on proteins", *Science*, 219:660-666. Peptides capable of eliciting protein-reactive sera are frequently represented in the primary sequence of a protein, can be characterized by a set of simple chemical rules, and are confined neither to immunodominant regions of intact proteins (i.e., immunogenic epitopes) nor to the amino or carboxyl terminals. Antigenic epitope-bearing peptides and polypeptides of the invention are therefore useful to raise antibodies, including monoclonal antibodies, that bind specifically to a polypeptide of the invention. See, for instance, Wilson et al., *Cell* 37:767-778 (1984) at 777.

In specific embodiments, antibodies of the present invention bind antigenic epitope-bearing peptides and polypeptides of B Lymphocyte Stimulator and preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids contained within the amino acid sequence of a B Lymphocyte Stimulator polypeptide. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof.

Non-limiting examples of antigenic polypeptides or peptides that can be used to generate B Lymphocyte Stimulator-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-115 to about Leu-147 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-150 to about Tyr-163 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-171 to about Phe-194 in SEQ ID NO:3228; a polypeptide

comprising, or alternatively consisting of, amino acid residues from about Glu-223 to about Tyr-246 in SEQ ID NO:3228; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-271 to about Phe-278 in FIGS. 1A and 1B (SEQ ID NO:3228). In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini. These polypeptide fragments have been determined to bear antigenic epitopes of the B Lymphocyte Stimulator polypeptide by the analysis of the Jameson-Wolf antigenic index, as disclosed Table 9, above.

Non-limiting examples of antigenic polypeptides or peptides that can be used to generate B Lymphocyte Stimulator-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-32 to about Leu-47 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-116 to about Ser-143 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-153 to about Tyr-173 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-218 to about Tyr-227 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ala-232 to about Gln-241 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-244 to about Ala-249 in SEQ ID NO:3229; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-252 to about Val-257 in SEQ ID NO:3229. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini. These polypeptide fragments have been determined to bear antigenic epitopes of the B Lymphocyte Stimulator polypeptide by the analysis of the Jameson-Wolf antigenic index, as disclosed in Table 10 generated by the Protean component of the DNA\*STAR computer program (as set forth above).

B Lymphocyte Stimulator epitope-bearing peptides and polypeptides may be produced by any conventional means. See, e.g., Houghten, R. A. (1985) General method for the rapid solid-phase synthesis of large numbers of peptides: specificity of antigen-antibody interaction at the level of individual amino acids. *Proc. Natl. Acad. Sci. USA* 82:5131-5135; this "Simultaneous Multiple Peptide Synthesis (SMPS)" process is further described in U.S. Pat. No. 4,631,211 to Houghten et al. (1986).

The present invention encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3228, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC™ deposit No. 97768, or encoded by a polynucleotide that

hybridizes to cDNA sequence contained in ATCC™ deposit No. 97768 (e.g., under hybridization conditions described herein).

The present invention also encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3229, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC™ deposit No. 203518, or encoded by a polynucleotide that hybridizes to the cDNA sequence contained in ATCC™ deposit No. 203518 (e.g., under hybridization conditions described herein).

The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses antibodies that bind a polypeptide comprising an epitope. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geyseu et al., *Proc. Natl. Acad. Sci. USA* 81:3998-4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross-reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

B Lymphocyte Stimulator polypeptide fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, *Proc. Natl. Acad. Sci. USA* 82:5131-5135 (1985), further described in U.S. Pat. No. 4,631,211).

In the present invention, antibodies of the present invention bind antigenic epitopes preferably containing a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes that may be bound by antibodies of the present invention are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., *Cell* 37:767-778 (1984); Sutcliffe et al., *Science* 219:660-666 (1983)).

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., *Proc. Natl. Acad. Sci. USA* 82:910-914; and Bittle et al., *J. Gen. Virol.* 66:2347-2354 (1985)). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immu-

nogenic epitopes of B Lymphocyte Stimulator may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing B Lymphocyte Stimulator polypeptides may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., *J. Gen. Virol.*, 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody title may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemocyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimido-benzoyl-N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier-coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 micrograms of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the antibodies of the present invention may bind polypeptides comprising an immunogenic or antigenic epitope fused to other polypeptide sequences. For example, the B Lymphocyte Stimulator polypeptides may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof), or albumin (including but not limited to recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Pat. No. 5,876,969, issued Mar. 2, 1999, EP Patent 0 413 622, and U.S. Pat. No. 5,766,883, issued Jun. 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Trautnecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof

alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270: 3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8972-8977). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix-binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto  $\text{Ni}^{2+}$  nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

In another embodiment, the antibodies of the present invention bind B Lymphocyte Stimulator polypeptides and/or the epitope-bearing fragments thereof that are fused with a heterologous antigen (e.g., polypeptide, carbohydrate, phospholipid, or nucleic acid). In specific embodiments, the heterologous antigen is an immunogen.

In a more specific embodiment, the heterologous antigen is the gp120 protein of HIV, or a fragment thereof.

In another embodiment, antibodies of the present invention bind B Lymphocyte Stimulator polypeptides and/or the epitope-bearing fragments thereof that are fused with polypeptide sequences of another TNF ligand family member (or biologically active fragments or variants thereof). In a specific embodiment, the antibodies of the present invention bind B Lymphocyte Stimulator polypeptides of the present invention are fused with a CD40L polypeptide sequence. In a preferred embodiment, the CD40L polypeptide sequence is soluble.

In another embodiment, antibodies of the present invention bind mutant B Lymphocyte Stimulator polypeptides that have been generated by random mutagenesis of a polynucleotide encoding the B Lymphocyte Stimulator polypeptide, by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, antibodies of the present invention bind one or more components, motifs, sections, parts, domains, fragments, etc., of B Lymphocyte Stimulator recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are, for example, TNF- $\alpha$ , lymphotxin- $\alpha$  (LT- $\alpha$ , also known as TNF- $\beta$ ), LT- $\beta$  (found in complex heterotrimeric LT- $\alpha$ 2- $\beta$ 2), OPG, FasL, CD27L, CD30L, CD40L, 4-1BB, DeR3, OX40L, TNF- $\gamma$  (International Publication No. WO 96/14328), AIM-1 (International Publication No. WO 97/33899), AIM-II (International Publication No. WO 97/34911), APRIL (J. Exp. Med. 188(6): 1185-1190), endokine- $\alpha$  (International Publication No. WO 98/07880), OPG, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-1BB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication

No. WO 98/06842), TR12, CAD, and v-FLIP. In further embodiments, the heterologous molecules are any member of the TNF family.

In another preferred embodiment, antibodies of the present invention bind B Lymphocyte Stimulator polypeptides of the invention (including biologically active fragments or variants thereof), that are fused with soluble APRIL polypeptides (e.g., amino acid residues 105 through 250 of SEQ ID NO:3239), or biologically active fragments or variants thereof.

To improve or alter the characteristics of B Lymphocyte Stimulator polypeptides, protein engineering may be employed. Recombinant DNA technology known to those skilled in the art can be used to create novel mutant proteins or "mutants" including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions. For instance, for many proteins, including the extracellular domain or the mature form(s) of a secreted protein, it is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function. For instance, Ron et al., *J. Biol. Chem.*, 268:2984-2988 (1993) reported modified KGF proteins that had heparin binding activity even if 3, 8, or 27 amino-terminal amino acid residues were missing. Accordingly, antibodies of the present invention may bind B Lymphocyte Stimulator polypeptide mutants or variants generated by protein engineering.

In the present case, since the protein of the invention is a member of the TNF polypeptide family, deletions of N-terminal amino acids up to the Gly (G) residue at position 191 in SEQ ID NO:3228 may retain some biological activity such as, for example, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and cytotoxicity to appropriate target cells. Polypeptides having further N-terminal deletions including the Gly (G) residue would not be expected to retain biological activities because it is known that this residue in TNF-related polypeptides is in the beginning of the conserved domain required for biological activities. However, even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities may still be retained. Thus, the ability of the shortened protein to induce and/or bind to antibodies which recognize the complete or extracellular domain of the protein generally will be retained when less than the majority of the residues of the complete or extracellular domain of the protein are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the B Lymphocyte Stimulator of SEQ ID NO:3228, up to the glycine residue at position 191 (Gly-191 residue from the amino terminus). In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n'-285 of SEQ ID NO:3228, where n' is an integer in the range of the amino acid position of amino acid residues 2-190 of the amino acid sequence in SEQ ID

NO:3228. More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues 2-285, 3-285, 4-285, 5-285, 6-285, 7-285, 8-285, 9-285, 10-285, 11-285, 12-285, 13-285, 14-285, 15-285, 16-285, 17-285, 18-285, 19-285, 20-285, 21-285, 22-285, 23-285, 24-285, 25-285, 26-285, 27-285, 28-285, 29-285, 30-285, 31-285, 32-285, 33-285, 34-285, 35-285, 36-285, 37-285, 38-285, 39-285, 40-285, 41-285, 42-285, 43-285, 44-285, 45-285, 46-285, 47-285, 48-285, 49-285, 50-285, 51-285, 52-285, 53-285, 54-285, 55-285, 56-285, 57-285, 58-285, 59-285, 60-285, 61-285, 62-285, 63-285, 64-285, 65-285, 66-285, 67-285, 68-285, 69-285, 70-285, 71-285, 72-285, 73-285, 74-285, 75-285, 76-285, 77-285, 78-285, 79-285, 80-285, 81-285, 82-285, 83-285, 84-285, 85-285, 86-285, 87-285, 88-285, 89-285, 90-285, 91-285, 92-285, 93-285, 94-285, 95-285, 96-285, 97-285, 98-285, 99-285, 100-285, 101-285, 102-285, 103-285, 104-285, 105-285, 106-285, 107-285, 108-285, 109-285, 110-285, 111-285, 112-285, 113-285, 114-285, 115-285, 116-285, 117-285, 118-285, 119-285, 120-285, 121-285, 122-285, 123-285, 124-285, 125-285, 126-285, 127-285, 128-285, 129-285, 130-285, 131-285, 132-285, 133-285, 134-285, 135-285, 136-285, 137-285, 138-285, 139-285, 140-285, 141-285, 142-285, 143-285, 144-285, 145-285, 146-285, 147-285, 148-285, 149-285, 150-285, 151-285, 152-285, 153-285, 154-285, 155-285, 156-285, 157-285, 158-285, 159-285, 160-285, 161-285, 162-285, 163-285, 164-285, 165-285, 166-285, 167-285, 168-285, 169-285, 170-285, 171-285, 172-285, 173-285, 174-285, 175-285, 176-285, 177-285, 178-285, 179-285, 180-285, 181-285, 182-285, 183-285, 184-285, 185-285, 186-285, 187-285, 188-285, 189-285, and 190-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

Furthermore, since the predicted extracellular domain of the B Lymphocyte Stimulator polypeptides of the invention may itself elicit biological activity, deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide (spanning positions Gln-73 to Leu-285 of SEQ ID NO:3228) may retain some biological activity such as, for example, ligand binding, stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication or modulation of target cell activities. However, even if deletion of one or more amino acids from the N-terminus of the predicted extracellular domain of a B Lymphocyte Stimulator polypeptide results in modification or loss of one or more biological functions of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues

deleted from the amino terminus of the amino acid sequence of B Lymphocyte Stimulator shown in SEQ ID NO:3228, up to the glycine residue at position number 280. In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n<sup>o</sup>-285 of SEQ ID NO:3228, where n<sup>o</sup> is an integer in the range of the amino acid position of amino acid residues 73-280 in SEQ ID NO:3228, and 73 is the position of the first residue from the N-terminus of the predicted extracellular domain of the B Lymphocyte Stimulator polypeptide (disclosed in SEQ ID NO:3228). More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of Q-73 to L-285; G-74 to L-285; D-75 to L-285; L-76 to L-285; A-77 to L-285; S-78 to L-285; L-79 to L-285; R-80 to L-285; A-81 to L-285; E-82 to L-285; L-83 to L-285; Q-84 to L-285; G-85 to L-285; H-86 to L-285; H-87 to L-285; A-88 to L-285; E-89 to L-285; K-90 to L-285; L-91 to L-285; P-92 to L-285; A-93 to L-285; G-94 to L-285; A-95 to L-285; G-96 to L-285; A-97 to L-285; P-98 to L-285; K-99 to L-285; A-100 to L-285; G-101 to L-285; L-102 to L-285; E-103 to L-285; E-104 to L-285; A-105 to L-285; P-106 to L-285; A-107 to L-285; V-108 to L-285; T-109 to L-285; A-110 to L-285; G-111 to L-285; L-112 to L-285; K-113 to L-285; L-114 to L-285; F-115 to L-285; E-116 to L-285; P-117 to L-285; P-118 to L-285; A-119 to L-285; P-120 to L-285; G-121 to L-285; E-122 to L-285; G-123 to L-285; N-124 to L-285; S-125 to L-285; S-126 to L-285; Q-127 to L-285; N-128 to L-285; S-129 to L-285; R-130 to L-285; N-131 to L-285; K-132 to L-285; R-133 to L-285; A-134 to L-285; V-135 to L-285; Q-136 to L-285; G-137 to L-285; P-138 to L-285; E-139 to L-285; E-140 to L-285; T-141 to L-285; V-142 to L-285; T-143 to L-285; Q-144 to L-285; D-145 to L-285; C-146 to L-285; L-147 to L-285; Q-148 to L-285; L-149 to L-285; I-150 to L-285; A-151 to L-285; D-152 to L-285; S-153 to L-285; E-154 to L-285; T-155 to L-285; P-156 to L-285; T-157 to L-285; I-158 to L-285; Q-159 to L-285; K-160 to L-285; G-161 to L-285; S-162 to L-285; Y-163 to L-285; T-164 to L-285; F-165 to L-285; V-166 to L-285; P-167 to L-285; W-168 to L-285; L-169 to L-285; L-170 to L-285; S-171 to L-285; F-172 to L-285; K-173 to L-285; R-174 to L-285; G-175 to L-285; S-176 to L-285; A-177 to L-285; L-178 to L-285; E-179 to L-285; E-180 to L-285; K-181 to L-285; E-182 to L-285; N-183 to L-285; K-184 to L-285; I-185 to L-285; L-186 to L-285; V-187 to L-285; K-188 to L-285; E-189 to L-285; T-190 to L-285; G-191 to L-285; Y-192 to L-285; F-193 to L-285; F-194 to L-285; I-195 to L-285; Y-196 to L-285; G-197 to L-285; Q-198 to L-285; V-199 to L-285; L-200 to L-285; Y-201 to L-285; T-202 to L-285; D-203 to L-285; K-204 to L-285; T-205 to L-285; Y-206 to L-285; A-207 to L-285; M-208 to L-285; G-209 to L-285; H-210 to L-285; L-211 to L-285; I-212 to L-285; Q-213 to L-285; R-214 to L-285; K-215 to L-285; K-216 to L-285; V-217 to L-285; H-218 to L-285; V-219 to L-285; F-220 to L-285; G-221 to L-285; D-222 to L-285; E-223 to L-285; L-224 to L-285; S-225 to L-285; L-226 to L-285; V-227 to L-285; T-228 to L-285; L-229 to L-285; F-230 to L-285; R-231 to L-285; C-232 to L-285; I-233 to L-285; Q-234 to L-285; N-235 to L-285; M-236 to L-285; P-237 to L-285; E-238 to L-285; T-239 to L-285; L-240 to L-285; P-241 to L-285; N-242 to L-285; N-243 to L-285; S-244 to L-285; C-245 to L-285; Y-246 to L-285; S-247 to L-285; A-248 to L-285; G-249 to L-285; I-250 to L-285; A-251 to L-285; K-252 to L-285; L-253 to L-285; E-254 to L-285; E-255 to L-285; G-256 to L-285; D-257 to L-285;

E-258 to L-285; L-259 to L-285; Q-260 to L-285; L-261 to L-285; A-262 to L-285; 1-263 to L-285; P-264 to L-285; R-265 to L-285; E-266 to L-285; N-267 to L-285; A-268 to L-285; Q-269 to L-285; 1-270 to L-285; S-271 to L-285; L-272 to L-285; D-273 to L-285; G-274 to L-285; D-275 to L-285; V-276 to L-285; T-277 to L-285; F-278 to L-285; F-279 to L-285; and G-280 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

Highly preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence least 80%, 85%, 90% identical and more preferably at least 95%, 96%, 97%, 98%, 99% or 100% identical to B Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

Preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 90% identical to a B Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 95% identical to a B Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 96% identical to a B Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 97% to a B Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 98% to a B Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 99% identical to B Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

In specific embodiments, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, one of the following N-terminally deleted polypeptide fragments of B Lymphocyte Stimulator: amino acid residues Ala-71 through Leu-285, amino acid residues Ala-81 through Leu-285, amino acid residues Leu-112 through Leu-285, amino acid residues Ala-134 through Leu-285, amino acid residues Leu-147 through Leu-285, and amino acid residues Gly-161 through Leu-285 of SEQ ID NO:3228.

Similarly, many examples of biologically functional C-terminal deletion polypeptides are known. For instance, Interferon gamma shows up to ten times higher activities by deleting 8-10 amino acid residues from the carboxy terminus of the protein (Döbel et al., *J. Biotechnology* 7:199-216 (1988)). Since the present protein is a member of the TNF polypeptide family, deletions of C-terminal amino acids up to the leucine residue at position 284 are expected to retain most if not all biological activity such as, for example, ligand binding, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication. Polypeptides having deletions of up to about 10 additional C-terminal residues (i.e., up to the glycine residue at position 274) also may retain some activity such as receptor binding, although such polypeptides would lack a portion of the conserved TNF domain which extends to about Leu-284 of SEQ ID NO:3228. However, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities may still be retained. Thus, the ability of the shortened protein to induce and/or bind to antibodies which recognize the complete or mature protein generally will be retained when less than the majority of the residues of the complete or mature protein are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete protein retains such immunological activities can readily be determined by routine methods described herein and otherwise known in the art.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the B Lymphocyte Stimulator polypeptide of SEQ ID NO:3228, up to the glycine residue at position 274 (Gly-274). In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 1-m of the amino acid sequence in SEQ ID NO:3228, where m<sup>1</sup> is any integer in the range of the amino acid position of amino acid residues 274-284 in SEQ ID NO:3228. More in particular, the invention provides antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues 1-274, 1-275, 1-276, 1-277, 1-278, 1-279, 1-280, 1-281, 1-282, 1-283 and 1-284 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

Also provided are antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively consisting of, B Lymphocyte Stimulator polypeptides with one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues n<sup>1</sup>-m<sup>1</sup> of SEQ ID NO:3228, where n<sup>1</sup> and m<sup>1</sup> are integers as defined above. Also included are antibodies that bind a polypeptide comprising, or alternatively consisting of, a portion of the complete B Lymphocyte Stimulator amino acid sequence encoded by the deposited cDNA clone contained in ATCC<sup>TM</sup> Accession No. 97768 where this portion excludes from 1 to 190 amino acids from the amino terminus or from 1 to 11 amino acids from the C-terminus of the complete amino acid sequence (or any combination of



these N-terminal and C-terminal deletions) encoded by the cDNA clone in the deposited plasmid.

Similarly, deletions of C-terminal amino acid residues of the predicted extracellular domain of B Lymphocyte Stimulator up to the leucine residue at position 79 of SEQ ID NO:3228 may retain some biological activity, such as, for example, ligand binding, stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication or modulation of target cell activities. Polypeptides having further C-terminal deletions including Leu-79 of SEQ ID NO:3228 would not be expected to retain biological activities.

However, even if deletion of one or more amino acids from the C-terminus of a polypeptide results in modification or loss of one or more biological functions of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete, mature or extracellular forms of the polypeptide generally will be retained when less than the majority of the residues of the complete, mature or extracellular forms of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of the predicted extracellular domain retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the predicted extracellular domain of B Lymphocyte Stimulator polypeptide shown in SEQ ID NO:3228, up to the leucine residue at position 79 of SEQ ID NO:3228. In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 73-m<sup>2</sup> of the amino acid sequence in SEQ ID NO:3228, where m<sup>2</sup> is any integer in the range of the amino acid position of amino acid residues 79 to 285 in the amino acid sequence in SEQ ID NO:3228, and residue 78 is the position of the first residue at the C-terminus of the predicted extracellular domain of the B Lymphocyte Stimulator polypeptide (disclosed in SEQ ID NO:3228). More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues 73 to Leu-285; 73 to L-284; 73 to K-283; 73 to L-282; 73 to A-281; 73 to G-280; 73 to F-279; 73 to F-278; 73 to T-277; 73 to V-276; 73 to D-275; 73 to G-274; 73 to D-273; 73 to L-272; 73 to S-271; 73 to L-270; 73 to Q-269; 73 to A-268; 73 to N-267; 73 to R-266; 73 to R-265; 73 to P-264; 73 to L-263; 73 to A-262; 73 to L-261; 73 to Q-260; 73 to L-259; 73 to E-258; 73 to D-257; 73 to G-256; 73 to E-255; 73 to E-254; 73 to L-253; 73 to K-252; 73 to A-251; 73 to Q-250; 73 to G-249; 73 to A-248; 73 to S-247; 73 to Y-246; 73 to C-245; 73 to S-244; 73 to N-243; 73 to N-242; 73 to P-241; 73 to L-240; 73 to T-239; 73 to E-238; 73 to P-237; 73 to M-236; 73 to N-235; 73 to Q-234; 73 to L-233; 73 to C-232; 73 to R-231; 73 to F-230; 73 to L-229; 73 to T-228; 73 to V-227; 73 to L-226; 73 to S-225; 73 to L-224; 73 to E-223; 73 to D-222; 73 to G-221; 73 to F-220; 73 to V-219; 73 to H-218; 73 to V-217; 73 to K-216; 73 to K-215; 73 to R-214; 73 to Q-213; 73 to L-212; 73 to L-211; 73 to H-210; 73 to G-209; 73 to M-208; 73 to A-207; 73 to Y-206; 73 to

T-205; 73 to K-204; 73 to D-203; 73 to T-202; 73 to Y-201; 73 to L-200; 73 to V-199; 73 to Q-198; 73 to G-197; 73 to Y-196; 73 to L-195; 73 to P-194; 73 to F-193; 73 to Y-192; 73 to G-191; 73 to T-190; 73 to E-189; 73 to K-188; 73 to V-187; 73 to L-186; 73 to L-185; 73 to K-184; 73 to N-183; 73 to E-182; 73 to K-181; 73 to E-180; 73 to E-179; 73 to L-178; 73 to A-177; 73 to S-176; 73 to G-175; 73 to R-174; 73 to K-173; 73 to F-172; 73 to S-171; 73 to L-170; 73 to L-169; 73 to W-168; 73 to P-167; 73 to V-166; 73 to F-165; 73 to T-164; 73 to Y-163; 73 to S-162; 73 to G-161; 73 to K-160; 73 to Q-159; 73 to L-158; 73 to T-157; 73 to P-156; 73 to T-155; 73 to E-154; 73 to S-153; 73 to D-152; 73 to A-151; 73 to L-150; 73 to L-149; 73 to Q-148; 73 to L-147; 73 to C-146; 73 to D-145; 73 to Q-144; 73 to T-143; 73 to V-142; 73 to T-141; 73 to E-140; 73 to E-139; 73 to P-138; 73 to G-137; 73 to Q-136; 73 to V-135; 73 to A-134; 73 to R-133; 73 to K-132; 73 to N-131; 73 to R-130; 73 to S-129; 73 to N-128; 73 to Q-127; 73 to S-126; 73 to S-125; 73 to N-124; 73 to G-123; 73 to E-122; 73 to G-121; 73 to P-120; 73 to A-119; 73 to P-118; 73 to P-117; 73 to E-116; 73 to F-115; 73 to L-114; 73 to K-113; 73 to L-112; 73 to G-111; 73 to A-110; 73 to T-109; 73 to V-108; 73 to A-107; 73 to P-106; 73 to A-105; 73 to E-104; 73 to E-103; 73 to L-102; 73 to G-101; 73 to A-100; 73 to K-99; 73 to P-98; 73 to A-97; 73 to G-96; 73 to A-95; 73 to G-94; 73 to A-93; 73 to P-92; 73 to L-91; 73 to K-90; 73 to E-89; 73 to A-88; 73 to H-87; 73 to H-86; 73 to G-85; 73 to Q-84; 73 to L-83; 73 to E-82; 73 to A-81; 73 to R-80; and 73 to L-79 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of the predicted extracellular domain of B Lymphocyte Stimulator, which may be described generally as having residues n<sup>2</sup>-m<sup>2</sup> of SEQ ID NO:3228 where n<sup>2</sup> and m<sup>2</sup> are integers as defined above.

In another embodiment, antibodies of the present invention bind polypeptides consisting of a portion of the extracellular domain of the B Lymphocyte Stimulator amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC™ accession no. 97768, where this portion excludes from 1 to about 206 amino acids from the amino terminus of the extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC™ accession no. 97768, or from 1 to about 206 amino acids from the carboxy terminus of the extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC™ accession no. 97768, or any combination of the above amino terminal and carboxy terminal deletions, of the entire extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC™ accession no. 97768.

As mentioned above, even if deletion of one or more amino acids from the N-terminus of a polypeptide results in modification or loss of one or more functional activities

(e.g., biological activity) of the polypeptide, other functions or biological activities may still be retained. Thus, the ability of a shortened B Lymphocyte Stimulator protein to induce and/or bind to antibodies which recognize the full-length or mature forms or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the full-length or mature or extracellular domain of the polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a B Lymphocyte Stimulator protein with a large number of deleted N-terminal amino acid residues may retain some functional (e.g., biological or immunogenic) activities. In fact, peptides composed of as few as six B Lymphocyte Stimulator amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the predicted full-length amino acid sequence of the B Lymphocyte Stimulator shown in SEQ ID NO:3228, up to the glycine residue at position number 280 of the sequence shown SEQ ID NO:3228 and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n<sup>3</sup>-285 of the sequence shown in SEQ ID NO:3228, where n<sup>3</sup> is an integer in the range of the amino acid position of amino acid residues 1 to 280 of the amino acid sequence in SEQ ID NO:3228.

More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of D-2 to L-285; D-3 to L-285; S-4 to L-285; T-5 to L-285; E-6 to L-285; R-7 to L-285; E-8 to L-285; Q-9 to L-285; S-10 to L-285; R-11 to L-285; L-12 to L-285; T-13 to L-285; S-14 to L-285; C-15 to L-285; L-16 to L-285; K-17 to L-285; K-18 to L-285; R-19 to L-285; E-20 to L-285; E-21 to L-285; M-22 to L-285; K-23 to L-285; L-24 to L-285; K-25 to L-285; E-26 to L-285; C-27 to L-285; V-28 to L-285; S-29 to L-285; I-30 to L-285; L-31 to L-285; P-32 to L-285; R-33 to L-285; K-34 to L-285; E-35 to L-285; S-36 to L-285; P-37 to L-285; S-38 to L-285; V-39 to L-285; R-40 to L-285; S-41 to L-285; S-42 to L-285; K-43 to L-285; D-44 to L-285; G-45 to L-285; K-46 to L-285; L-47 to L-285; L-48 to L-285; A-49 to L-285; A-50 to L-285; T-51 to L-285; L-52 to L-285; L-53 to L-285; L-54 to L-285; A-55 to L-285; L-56 to L-285; L-57 to L-285; S-58 to L-285; C-59 to L-285; C-60 to L-285; L-61 to L-285; T-62 to L-285; V-63 to L-285; V-64 to L-285; S-65 to L-285; F-66 to L-285; Y-67 to L-285; Q-68 to L-285; V-69 to L-285; A-70 to L-285; A-71 to L-285; L-72 to L-285; Q-73 to L-285; G-74 to L-285; D-75 to L-285; L-76 to L-285; A-77 to L-285; S-78 to L-285; L-79 to L-285; R-80 to L-285; A-81 to L-285; E-82 to L-285; L-83 to L-285; Q-84 to L-285; G-85 to L-285; H-86 to L-285; H-87 to L-285; A-88 to L-285; E-89 to L-285; K-90 to L-285; L-91 to L-285; P-92 to L-285; A-93 to L-285; G-94 to L-285; A-95 to L-285; G-96 to L-285; A-97 to L-285; P-98 to L-285; K-99 to L-285; A-100 to L-285; G-101 to L-285; L-102 to L-285; E-103 to L-285; E-104 to L-285; A-105 to L-285; P-106 to L-285; A-107 to L-285; V-108 to L-285; T-109 to L-285; A-110 to L-285; G-111 to L-285; L-112 to L-285; K-113 to L-285; I-114 to L-285; F-115 to L-285; E-116 to L-285; P-117 to L-285; P-118 to L-285; A-119 to L-285; P-120 to L-285; G-121 to L-285; E-122 to L-285; G-123 to L-285;

N-124 to L-285; S-125 to L-285; S-126 to L-285; Q-127 to L-285; N-128 to L-285; S-129 to L-285; R-130 to L-285; N-131 to L-285; K-132 to L-285; R-133 to L-285; A-134 to L-285; V-135 to L-285; Q-136 to L-285; G-137 to L-285; P-138 to L-285; E-139 to L-285; E-140 to L-285; T-141 to L-285; V-142 to L-285; T-143 to L-285; Q-144 to L-285; D-145 to L-285; C-146 to L-285; L-147 to L-285; Q-148 to L-285; L-149 to L-285; I-150 to L-285; A-151 to L-285; D-152 to L-285; S-153 to L-285; E-154 to L-285; T-155 to L-285; P-156 to L-285; T-157 to L-285; L-158 to L-285; Q-159 to L-285; K-160 to L-285; G-161 to L-285; S-162 to L-285; Y-163 to L-285; T-164 to L-285; F-165 to L-285; V-166 to L-285; P-167 to L-285; W-168 to L-285; L-169 to L-285; L-170 to L-285; S-171 to L-285; F-172 to L-285; K-173 to L-285; R-174 to L-285; G-175 to L-285; S-176 to L-285; A-177 to L-285; L-178 to L-285; E-179 to L-285; E-180 to L-285; K-181 to L-285; E-182 to L-285; N-183 to L-285; K-184 to L-285; I-185 to L-285; L-186 to L-285; V-187 to L-285; K-188 to L-285; E-189 to L-285; T-190 to L-285; G-191 to L-285; Y-192 to L-285; F-193 to L-285; F-194 to L-285; I-195 to L-285; Y-196 to L-285; G-197 to L-285; Q-198 to L-285; V-199 to L-285; L-200 to L-285; Y-201 to L-285; T-202 to L-285; D-203 to L-285; K-204 to L-285; T-205 to L-285; Y-206 to L-285; A-207 to L-285; M-208 to L-285; G-209 to L-285; H-210 to L-285; L-211 to L-285; I-212 to L-285; Q-213 to L-285; R-214 to L-285; K-215 to L-285; K-216 to L-285; V-217 to L-285; H-218 to L-285; V-219 to L-285; F-220 to L-285; G-221 to L-285; D-222 to L-285; E-223 to L-285; L-224 to L-285; S-225 to L-285; L-226 to L-285; V-227 to L-285; T-228 to L-285; L-229 to L-285; F-230 to L-285; R-231 to L-285; C-232 to L-285; I-233 to L-285; Q-234 to L-285; N-235 to L-285; M-236 to L-285; P-237 to L-285; E-238 to L-285; T-239 to L-285; L-240 to L-285; P-241 to L-285; N-242 to L-285; N-243 to L-285; S-244 to L-285; C-245 to L-285; Y-246 to L-285; S-247 to L-285; A-248 to L-285; G-249 to L-285; L-250 to L-285; A-251 to L-285; K-252 to L-285; L-253 to L-285; E-254 to L-285; E-255 to L-285; G-256 to L-285; D-257 to L-285; E-258 to L-285; L-259 to L-285; Q-260 to L-285; L-261 to L-285; A-262 to L-285; I-263 to L-285; P-264 to L-285; R-265 to L-285; E-266 to L-285; N-267 to L-285; A-268 to L-285; Q-269 to L-285; I-270 to L-285; S-271 to L-285; L-272 to L-285; D-273 to L-285; G-274 to L-285; D-275 to L-285; V-276 to L-285; T-277 to L-285; F-278 to L-285; F-279 to L-285; and G-280 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more functional activities (e.g., biological activity) of the protein, other functional activities may still be retained. Thus, the ability of a shortened B Lymphocyte Stimulator protein to induce and/or bind to antibodies which recognize the complete or mature form or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature form or the extracellular domain of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a B

Lymphocyte Stimulator mutein with a large number of deleted C-terminal amino acid residues may retain some functional (e.g., biological or immunogenic) activities. In fact, peptides composed of as few as six B Lymphocyte Stimulator amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides in another embodiment, antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the B Lymphocyte Stimulator shown in SEQ ID NO:3228, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1- $m^3$  of SEQ ID NO:3228, where  $m^3$  is an integer in the range of the amino acid position of amino acid residues 6-284 of the amino acid sequence in SEQ ID NO:3228.

More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-284; M-1 to K-283; M-1 to L-282; M-1 to A-281; M-1 to G-280; M-1 to F-279; M-1 to F-278; M-1 to T-277; M-1 to V-276; M-1 to D-275; M-1 to G-274; M-1 to D-273; M-1 to L-272; M-1 to S-271; M-1 to L-270; M-1 to Q-269; M-1 to A-268; M-1 to N-267; M-1 to E-266; M-1 to R-265; M-1 to P-264; M-1 to L-263; M-1 to A-262; M-1 to L-261; M-1 to Q-260; M-1 to L-259; M-1 to E-258; M-1 to D-257; M-1 to G-256; M-1 to E-255; M-1 to E-254; M-1 to L-253; M-1 to K-252; M-1 to A-251; M-1 to L-250; M-1 to G-249; M-1 to A-248; M-1 to S-247; M-1 to Y-246; M-1 to C-245; M-1 to S-244; M-1 to N-243; M-1 to N-242; M-1 to P-241; M-1 to L-240; M-1 to T-239; M-1 to E-238; M-1 to P-237; M-1 to M-236; M-1 to N-235; M-1 to Q-234; M-1 to I-233; M-1 to C-232; M-1 to R-231; M-1 to F-230; M-1 to L-229; M-1 to T-228; M-1 to V-227; M-1 to L-226; M-1 to S-225; M-1 to L-224; M-1 to E-223; M-1 to D-222; M-1 to G-221; M-1 to F-220; M-1 to V-219; M-1 to H-218; M-1 to V-217; M-1 to K-216; M-1 to K-215; M-1 to R-214; M-1 to Q-213; M-1 to L-212; M-1 to L-211; M-1 to H-210; M-1 to G-209; M-1 to M-208; M-1 to A-207; M-1 to Y-206; M-1 to T-205; M-1 to K-204; M-1 to D-203; M-1 to T-202; M-1 to Y-201; M-1 to L-200; M-1 to V-199; M-1 to Q-198; M-1 to G-197; M-1 to Y-196; M-1 to L-195; M-1 to F-194; M-1 to F-193; M-1 to Y-192; M-1 to G-191; M-1 to T-190; M-1 to E-189; M-1 to K-188; M-1 to V-187; M-1 to L-186; M-1 to L-185; M-1 to K-184; M-1 to N-183; M-1 to E-182; M-1 to K-181; M-1 to E-180; M-1 to E-179; M-1 to L-178; M-1 to A-177; M-1 to S-176; M-1 to G-175; M-1 to R-174; M-1 to K-173; M-1 to F-172; M-1 to S-171; M-1 to L-170; M-1 to L-169; M-1 to W-168; M-1 to P-167; M-1 to V-166; M-1 to F-165; M-1 to T-164; M-1 to Y-163; M-1 to S-162; M-1 to G-161; M-1 to K-160; M-1 to Q-159; M-1 to L-158; M-1 to T-157; M-1 to P-156; M-1 to T-155; M-1 to E-154; M-1 to S-153; M-1 to D-152; M-1 to A-151; M-1 to L-150; M-1 to L-149; M-1 to Q-148; M-1 to L-147; M-1 to C-146; M-1 to D-145; M-1 to Q-144; M-1 to T-143; M-1 to V-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to L-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1

to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76; M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54; M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to L-16; M-1 to C-15; M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a B Lymphocyte Stimulator polypeptide, which may be described generally as having residues  $n^1$ - $m^3$  of SEQ ID NO:3228, where  $n^1$  and  $m^3$  are integers as defined above.

Furthermore, since the predicted extracellular domain of the B Lymphocyte Stimulator polypeptide of SEQ ID NO:3229 may itself elicit functional activity (e.g., biological activity), deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide at positions Hn-73 to Leu-266 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, to stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunogenicity. However, even if deletion of one or more amino acids from the N-terminus of the predicted extracellular domain of a B Lymphocyte Stimulator polypeptide results in modification or loss of one or more functional activities of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of B Lymphocyte Stimulator shown in SEQ ID NO:3229, up to the glycine residue at position number 261. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues  $n^1$ -266

of SEQ ID NO:3229, where  $n^4$  is an integer in the range of the amino acid position of amino acid residues 73-261 of the amino acid sequence in SEQ ID NO:3229, and 261 is the position of the first residue from the N-terminus of the predicted extracellular domain B Lymphocyte Stimulator polypeptide (shown in SEQ ID NO:3229).

More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101 to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to L-266; I-114 to L-266; P-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266; T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150 to L-266; L-151 to L-266; S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; I-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; I-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; L-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266; V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; L-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; G-228 to L-266; A-229 to L-266; G-230 to L-266; L-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240 to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; L-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to L-266; L-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid

residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

Similarly, deletions of C-terminal amino acid residues of the predicted extracellular domain of B Lymphocyte Stimulator up to the leucine residue at position 79 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunogenicity. Polypeptides having further C-terminal deletions including Leu-79 of SEQ ID NO:3229 would not be expected to retain biological activities.

However, even if deletion of one or more amino acids from the C-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete, mature or extracellular forms of the polypeptide generally will be retained when less than the majority of the residues of the complete, mature or extracellular forms of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of the predicted extracellular domain retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of the predicted extracellular domain of B Lymphocyte Stimulator shown in SEQ ID NO:3229, up to the leucine residue at position 79 of SEQ ID NO:3229. In particular, the present invention provides antibodies that bind polypeptides having the amino acid sequence of residues 73- $m^4$  of the amino acid sequence in SEQ ID NO:3229, where  $m^4$  is any integer in the range of the amino acid position of amino acid residues 79-265 of the amino acid sequence in SEQ ID NO:3229.

More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues Q-73 to L-265; Q-73 to K-264; Q-73 to L-263; Q-73 to A-262; Q-73 to G-261; Q-73 to F-260; Q-73 to F-259; Q-73 to T-258; Q-73 to Y-257; Q-73 to D-256; Q-73 to G-255; Q-73 to D-254; Q-73 to L-253; Q-73 to S-252; Q-73 to L-251; Q-73 to Q-250; Q-73 to A-249; Q-73 to N-248; Q-73 to E-247; Q-73 to R-246; Q-73 to P-245; Q-73 to L-244; Q-73 to A-243; Q-73 to L-242; Q-73 to Q-241; Q-73 to L-240; Q-73 to E-239; Q-73 to D-238; Q-73 to G-237; Q-73 to E-236; Q-73 to E-235; Q-73 to L-234; Q-73 to K-233; Q-73 to A-232; Q-73 to L-231; Q-73 to G-230; Q-73 to A-229; Q-73 to S-228; Q-73 to Y-227; Q-73 to C-226; Q-73 to S-225; Q-73 to N-224; Q-73 to N-223; Q-73 to P-222; Q-73 to L-221; Q-73 to T-220; Q-73 to E-219; Q-73 to P-218; Q-73 to M-217; Q-73 to N-216; Q-73 to Q-215; Q-73 to L-214; Q-73 to C-213; Q-73 to R-212; Q-73 to F-211; Q-73 to L-110; Q-73 to T-209; Q-73 to V-208; Q-73 to L-207; Q-73 to S-206; Q-73 to L-205; Q-73 to E-204; Q-73 to D-203; Q-73 to G-202; Q-73 to F-201; Q-73 to V-200; Q-73 to H-199; Q-73 to V-198; Q-73 to K-197; Q-73 to K-196; Q-73 to R-195; Q-73 to Q-194; Q-73 to L-193; Q-73 to L-192; Q-73 to H-191; Q-73 to G-190; Q-73 to Q-7389; Q-73 to A-188; Q-73 to Y-187; Q-73 to T-186; Q-73 to K-185; Q-73 to D-184; Q-73 to T-183; Q-73 to Y-182; Q-73 to L-181; Q-73 to Y-180; Q-73 to Q-179; Q-73 to G-178; Q-73 to Y-177;

Q-73 to L-176; Q-73 to F-175; Q-73 to F-174; Q-73 to Y-173; Q-73 to G-172; Q-73 to T-171; Q-73 to E-170; Q-73 to K-169; Q-73 to V-168; Q-73 to L-167; Q-73 to L-166; Q-73 to K-165; Q-73 to N-164; Q-73 to E-163; Q-73 to K-162; Q-73 to E-161; Q-73 to E-160; Q-73 to L-159; Q-73 to A-158; Q-73 to S-157; Q-73 to G-156; Q-73 to R-155; Q-73 to K-154; Q-73 to F-153; Q-73 to S-152; Q-73 to L-151; Q-73 to L-150; Q-73 to W-149; Q-73 to P-148; Q-73 to V-147; Q-73 to F-146; Q-73 to T-145; Q-73 to Y-144; Q-73 to S-143; Q-73 to G-142; Q-73 to T-141; Q-73 to E-140; Q-73 to E-139; Q-73 to P-138; Q-73 to G-137; Q-73 to Q-136; Q-73 to V-135; Q-73 to A-134; Q-73 to R-133; Q-73 to K-132; Q-73 to N-131; Q-73 to R-130; Q-73 to S-129; Q-73 to N-128; Q-73 to Q-127; Q-73 to S-126; Q-73 to S-125; Q-73 to N-124; Q-73 to G-123; Q-73 to E-122; Q-73 to G-121; Q-73 to P-120; Q-73 to A-119; Q-73 to P-118; Q-73 to P-117; Q-73 to E-116; Q-73 to F-115; Q-73 to L-114; Q-73 to K-113; Q-73 to L-112; Q-73 to G-111; Q-73 to A-110; Q-73 to T-109; Q-73 to V-108; Q-73 to A-107; Q-73 to P-106; Q-73 to A-105; Q-73 to E-104; Q-73 to E-103; Q-73 to L-102; Q-73 to G-101; Q-73 to A-100; Q-73 to K-99; Q-73 to P-98; Q-73 to A-97; Q-73 to G-96; Q-73 to A-95; Q-73 to G-94; Q-73 to A-93; Q-73 to P-92; Q-73 to L-91; Q-73 to K-90; Q-73 to F-89; Q-73 to A-88; Q-73 to H-87; Q-73 to H-86; Q-73 to G-85; Q-73 to Q-84; Q-73 to L-83; Q-73 to E-82; Q-73 to A-81; Q-73 to R-80; Q-73 to L-79; and Q-73 to S-78 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl terminus of the predicted extracellular domain of B Lymphocyte Stimulator, which may be described generally as having residues  $n^{\text{th}}$  of SEQ ID NO:3229 where  $n^{\text{th}}$  and  $m^{\text{th}}$  are integers as defined above.

In another embodiment, antibodies of the present invention bind polypeptides consisting of a portion of the extracellular domain of the B Lymphocyte Stimulator amino acid sequence encoded by the cDNA clone contained in the deposit having ATCC<sup>TM</sup> Accession No. 203518, where this portion excludes from 1 to about 260 amino acids from the amino terminus of the extracellular domain of the amino acid sequence encoded by cDNA clone contained in the deposit having ATCC<sup>TM</sup> Accession No. 203518, or from 1 to about 187 amino acids from the carboxy terminus of the extracellular domain of the amino acid sequence encoded by cDNA clone contained in the deposit having ATCC<sup>TM</sup> Accession No. 203518, or any combination of the above amino terminal and carboxy terminal deletions, of the entire extracellular domain of the amino acid sequence encoded by the cDNA clone contained in the deposit having ATCC<sup>TM</sup> Accession No. 203518.

As mentioned above, even if deletion of one or more amino acids from the N-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of a shortened B Lymphocyte Stimulator polypeptide to induce and/or bind to antibodies which recognize the full-length or mature forms or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the full-length or mature or extracellular domain of the polypeptide are removed from the N-terminus.

Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a B Lymphocyte Stimulator protein with a large number of deleted N-terminal amino acid residues may retain functional (e.g., immunogenic) activities. In fact, peptides composed of as few as six B Lymphocyte Stimulator amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the predicted full-length amino acid sequence of the B Lymphocyte Stimulator polypeptide shown in SEQ ID NO:3229, up to the glycine residue at position number 261 of the sequence shown SEQ ID NO:3229 and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues  $n^{\text{th}}$ -266 of the sequence shown in SEQ ID NO:3229, where  $n^{\text{th}}$  is an integer in the range of the amino acid position of amino acid residues 1 to 261 of the amino acid sequence in SEQ ID NO:3229.

More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of D-2 to L-266; D-3 to L-266; S-4 to L-266; T-5 to L-266; E-6 to L-266; R-7 to L-266; E-8 to L-266; Q-9 to L-266; S-10 to L-266; R-11 to L-266; L-12 to L-266; T-13 to L-266; S-14 to L-266; C-15 to L-266; L-16 to L-266; K-17 to L-266; K-18 to L-266; R-19 to L-266; E-20 to L-266; E-21 to L-266; M-22 to L-266; K-23 to L-266; L-24 to L-266; K-25 to L-266; E-26 to L-266; C-27 to L-266; V-28 to L-266; S-29 to L-266; I-30 to L-266; L-31 to L-266; P-32 to L-266; R-33 to L-266; K-34 to L-266; E-35 to L-266; S-36 to L-266; P-37 to L-266; S-38 to L-266; V-39 to L-266; R-40 to L-266; S-41 to L-266; S-42 to L-266; K-43 to L-266; D-44 to L-266; G-45 to L-266; K-46 to L-266; L-47 to L-266; L-48 to L-266; A-49 to L-266; A-50 to L-266; T-51 to L-266; L-52 to L-266; L-53 to L-266; L-54 to L-266; A-55 to L-266; L-56 to L-266; L-57 to L-266; S-58 to L-266; C-59 to L-266; C-60 to L-266; L-61 to L-266; T-62 to L-266; V-63 to L-266; V-64 to L-266; S-65 to L-266; F-66 to L-266; Y-67 to L-266; Q-68 to L-266; V-69 to L-266; A-70 to L-266; A-71 to L-266; L-72 to L-266; Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101 to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to L-266; L-114 to L-266; F-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266; T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150 to L-266; L-151 to L-266;

S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; L-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; L-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; L-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266; V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; L-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; S-228 to L-266; A-229 to L-266; G-230 to L-266; L-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240 to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; L-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to L-266; L-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more functional activities (e.g., biological activities) of the protein, other functional activities may still be retained. Thus, the ability of a shortened B Lymphocyte Stimulator protein to induce and/or bind to antibodies which recognize the complete or mature form or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature form or the extracellular domain of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a B Lymphocyte Stimulator protein with a large number of deleted C-terminal amino acid residues may retain some functional (e.g., immunogenic) activities. In fact, peptides composed of as few as six B Lymphocyte Stimulator amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides in another embodiment, antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the B Lymphocyte Stimulator shown in SEQ ID NO:3229, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1-m<sup>5</sup> of SEQ ID NO:3229, where m<sup>5</sup>

is an integer in the range of the amino acid position of amino acid residues 6 to 265 in the amino acid sequence of SEQ ID NO:3229.

More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-265; M-1 to K-264; M-1 to L-263; M-1 to A-262; M-1 to G-261; M-1 to F-260; M-1 to F-259; M-1 to T-258; M-1 to V-257; M-1 to D-256; M-1 to G-255; M-1 to D-254; M-1 to L-253; M-1 to S-252; M-1 to L-251; M-1 to Q-250; M-1 to A-249; M-1 to N-248; M-1 to E-247; M-1 to R-246; M-1 to P-245; M-1 to L-244; M-1 to A-243; M-1 to L-242; M-1 to Q-241; M-1 to L-240; M-1 to E-239; M-1 to D-238; M-1 to E-237; M-1 to E-236; M-1 to E-235; M-1 to L-234; M-1 to K-233; M-1 to A-232; M-1 to L-231; M-1 to G-230; M-1 to A-229; M-1 to S-228; M-1 to Y-227; M-1 to C-226; M-1 to S-225; M-1 to N-224; M-1 to N-223; M-1 to P-222; M-1 to L-221; M-1 to T-220; M-1 to E-219; M-1 to P-218; M-1 to M-217; M-1 to N-216; M-1 to Q-215; M-1 to L-214; M-1 to C-213; M-1 to R-212; M-1 to F-211; M-1 to L-210; M-1 to T-209; M-1 to V-208; M-1 to L-207; M-1 to S-206; M-1 to L-205; M-1 to E-204; M-1 to D-203; M-1 to G-202; M-1 to F-201; M-1 to V-200; M-1 to H-199; M-1 to V-198; M-1 to K-197; M-1 to K-196; M-1 to R-195; M-1 to Q-194; M-1 to L-193; M-1 to L-192; M-1 to H-191; M-1 to G-190; M-1 to M-189; M-1 to A-188; M-1 to Y-187; M-1 to T-186; M-1 to K-185; M-1 to D-184; M-1 to L-183; M-1 to Y-182; M-1 to L-181; M-1 to V-180; M-1 to Q-179; M-1 to G-178; M-1 to Y-177; M-1 to L-176; M-1 to F-175; M-1 to F-174; M-1 to Y-173; M-1 to G-172; M-1 to T-171; M-1 to E-170; M-1 to K-169; M-1 to V-168; M-1 to L-167; M-1 to L-166; M-1 to K-165; M-1 to N-164; M-1 to E-163; M-1 to K-162; M-1 to E-161; M-1 to E-160; M-1 to L-159; M-1 to A-158; M-1 to S-157; M-1 to G-156; M-1 to R-155; M-1 to K-154; M-1 to F-153; M-1 to S-152; M-1 to L-151; M-1 to L-150; M-1 to W-149; M-1 to P-148; M-1 to V-147; M-1 to F-146; M-1 to T-145; M-1 to Y-144; M-1 to S-143; M-1 to G-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to L-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1 to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76; M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54; M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to L-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to

L-16; M-1 to C-15; M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a B Lymphocyte Stimulator polypeptide, which may be described generally as having residues  $n^1$ - $m^1$  of SEQ ID NO:3229, where  $n^1$  and  $m^1$  are integers as defined above.

In additional embodiments, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 134- $m^2$  of SEQ ID NO:3228, where  $m^2$  is an integer from 140 to 285, corresponding to the position of the amino acid residue in SEQ ID NO:3228. For example, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues A-134 to Leu-285; A-134 to L-284; A-134 to K-283; A-134 to L-282; A-134 to A-281; A-134 to G-280; A-134 to F-279; A-134 to F-278; A-134 to T-277; A-134 to V-276; A-134 to D-275; A-134 to G-274; A-134 to D-273; A-134 to L-272; A-134 to S-271; A-134 to I-270; A-134 to Q-269; A-134 to A-268; A-134 to N-267; A-134 to E-266; A-134 to R-265; A-134 to P-264; A-134 to I-263; A-134 to A-262; A-134 to L-261; A-134 to Q-260; A-134 to L-259; A-134 to E-258; A-134 to D-257; A-134 to G-256; A-134 to E-255; A-134 to E-254; A-134 to L-253; A-134 to K-252; A-134 to A-251; A-134 to L-250; A-134 to G-249; A-134 to A-248; A-134 to S-247; A-134 to Y-246; A-134 to C-245; A-134 to S-244; A-134 to N-243; A-134 to N-242; A-134 to P-241; A-134 to L-240; A-134 to T-239; A-134 to E-238; A-134 to P-237; A-134 to M-236; A-134 to N-235; A-134 to Q-234; A-134 to I-233; A-134 to C-232; A-134 to R-231; A-134 to F-230; A-134 to L-229; A-134 to T-228; A-134 to V-227; A-134 to L-226; A-134 to S-225; A-134 to L-224; A-134 to E-223; A-134 to D-222; A-134 to G-221; A-134 to F-220; A-134 to V-219; A-134 to H-218; A-134 to V-217; A-134 to K-216; A-134 to K-215; A-134 to R-214; A-134 to Q-213; A-134 to I-212; A-134 to L-211; A-134 to H-210; A-134 to G-209; A-134 to M-208; A-134 to A-207; A-134 to Y-206; A-134 to T-205; A-134 to K-204; A-134 to D-203; A-134 to T-202; A-134 to Y-201; A-134 to L-200; A-134 to V-199; A-134 to Q-198; A-134 to G-197; A-134 to Y-196; A-134 to I-195; A-134 to F-194; A-134 to F-193; A-134 to Y-192; A-134 to G-191; A-134 to T-190; A-134 to E-189; A-134 to K-188; A-134 to V-187; A-134 to L-186; A-134 to I-185; A-134 to K-184; A-134 to N-183; A-134 to E-182; A-134 to K-181; A-134 to E-180; A-134 to E-179; A-134 to L-178; A-134 to A-177; A-134 to S-176; A-134 to G-175; A-134 to R-174; A-134 to K-173; A-134 to F-172; A-134 to S-171; A-134 to L-170; A-134 to L-169; A-134 to W-168; A-134 to P-167; A-134 to V-166; A-134 to F-165; A-134 to T-164; A-134 to Y-163; A-134 to S-162; A-134 to G-161; A-134 to K-160; A-134 to Q-159; A-134 to L-158; A-134 to T-157; A-134 to P-156; A-134 to T-155; A-134 to E-154; A-134 to S-153; A-134 to D-152; A-134 to A-151; A-134 to L-150; A-134 to L-149; A-134 to Q-148; A-134 to L-147; A-134 to C-146; A-134 to D-145; A-134 to Q-144; A-134 to T-143; A-134 to V-142; A-134 to T-141; and A-134 to E-140 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides com-

prising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to C-15; D-2 to L-16; D-3 to K-17; S-4 to K-18; T-5 to R-19; E-6 to E-20; R-7 to E-21; F-8 to M-22; Q-9 to K-23; S-10 to L-24; R-11 to K-25; L-12 to E-26; T-13 to C-27; S-14 to V-28; C-15 to S-29; L-16 to I-30; K-17 to L-31; K-18 to P-32; R-19 to R-33; E-20 to K-34; E-21 to E-35; M-22 to S-36; K-23 to P-37; L-24 to S-38; K-25 to V-39; E-26 to R-40; C-27 to S-41; V-28 to S-42; S-29 to K-43; I-30 to D-44; L-31 to G-45; P-32 to K-46; R-33 to L-47; K-34 to L-48; E-35 to A-49; S-36 to A-50; P-37 to T-51; S-38 to L-52; V-39 to L-53; R-40 to L-54; S-41 to A-55; S-42 to L-56; K-43 to L-57; D-44 to S-58; G-45 to C-59; K-46 to C-60; L-47 to L-61; L-48 to T-62; A-49 to V-63; A-50 to V-64; T-51 to S-65; L-52 to F-66; L-53 to Y-67; L-54 to Q-68; A-55 to V-69; L-56 to A-70; L-57 to A-71; S-58 to L-72; C-59 to Q-73; C-60 to G-74; L-61 to D-75; T-62 to L-76; V-63 to A-77; V-64 to S-78; S-65 to L-79; F-66 to R-80; Y-67 to A-81; Q-68 to E-82; V-69 to L-83; A-70 to Q-84; A-71 to G-85; L-72 to H-86; Q-73 to H-87; G-74 to A-88; D-75 to E-89; L-76 to K-90; A-77 to L-91; S-78 to P-92; L-79 to A-93; R-80 to G-94; A-81 to A-95; E-82 to G-96; L-83 to A-97; Q-84 to P-98; G-85 to K-99; H-86 to A-100; H-87 to G-101; A-88 to L-102; E-89 to E-103; K-90 to E-104; L-91 to A-105; P-92 to P-106; A-93 to A-107; G-94 to V-108; A-95 to T-109; G-96 to A-110; A-97 to G-111; P-98 to L-112; K-99 to K-113; A-100 to L-114; G-101 to F-115; L-102 to E-116; E-103 to P-117; E-104 to P-118; A-105 to A-119; P-106 to P-120; A-107 to G-121; V-108 to E-122; T-109 to G-123; A-110 to N-124; G-111 to S-125; L-112 to S-126; K-113 to Q-127; I-114 to N-128; F-115 to S-129; E-116 to R-130; P-117 to N-131; P-118 to K-132; A-119 to R-133; P-120 to A-134; G-121 to V-135; E-122 to Q-136; G-123 to G-137; N-124 to P-138; S-125 to E-139; S-126 to E-140; Q-127 to T-141; N-128 to V-142; S-129 to T-143; R-130 to Q-144; N-131 to D-145; K-132 to C-146; R-133 to L-147; A-134 to Q-148; V-135 to L-149; Q-136 to I-150; G-137 to A-151; P-138 to D-152; E-139 to S-153; E-140 to E-154; T-141 to T-155; V-142 to P-156; T-143 to T-157; Q-144 to I-158; D-145 to Q-159; C-146 to K-160; L-147 to G-161; Q-148 to S-162; L-149 to Y-163; I-150 to T-164; A-151 to F-165; D-152 to V-166; S-153 to P-167; E-154 to W-168; T-155 to L-169; P-156 to L-170; T-157 to S-171; I-158 to F-172; Q-159 to K-173; K-160 to R-174; G-161 to G-175; S-162 to S-176; Y-163 to L-177; T-164 to L-178; F-165 to E-179; V-166 to E-180; P-167 to K-181; W-168 to E-182; L-169 to N-183; L-170 to K-184; S-171 to I-185; F-172 to L-186; K-173 to V-187; R-174 to K-188; G-175 to E-189; S-176 to T-190; A-177 to G-191; L-178 to Y-192; E-179 to F-193; E-180 to F-194; K-181 to I-195; E-182 to Y-196; N-183 to G-197; K-184 to Q-198; I-185 to V-199; L-186 to L-200; V-187 to Y-201; K-188 to T-202; E-189 to D-203; T-190 to K-204; G-191 to T-205; Y-192 to Y-206; F-193 to A-207; F-194 to M-208; I-195 to G-209; Y-196 to H-210; G-197 to L-211; Q-198 to I-212; V-199 to Q-213; L-200 to R-214; Y-201 to K-215; T-202 to K-216; D-203 to V-217; K-204 to H-218; T-205 to V-219; Y-206 to F-220; A-207 to G-221; M-208 to D-222; G-209 to E-223; H-210 to L-224; L-211 to S-225; I-212 to L-226; Q-213 to V-227; R-214 to T-228; K-215 to L-229; K-216 to F-230; V-217 to

R-231; H-218 to C-232; V-219 to L-233; F-220 to Q-234; G-221 to N-235; D-222 to M-236; E-223 to P-237; L-224 to E-238; S-225 to T-239; L-226 to L-240; V-227 to P-241; T-228 to N-242; L-229 to N-243; F-230 to S-244; R-231 to C-245; C-232 to Y-246; L-233 to S-247; Q-234 to A-248; N-235 to G-249; M-236 to L-250; P-237 to A-251; E-238 to K-252; T-239 to L-253; L-240 to E-254; P-241 to E-255; N-242 to G-256; N-243 to D-257; S-244 to E-258; C-245 to L-259; Y-246 to Q-260; S-247 to L-261; A-248 to A-262; G-249 to L-263; L-250 to P-264; A-251 to R-265; K-252 to E-266; L-253 to N-267; E-254 to A-268; E-255 to Q-269; G-256 to L-270; D-257 to S-271; E-258 to L-272; L-259 to D-273; Q-260 to G-274; L-261 to D-275; A-262 to V-276; L-263 to T-277; P-264 to F-278; R-265 to F-279; F-266 to G-280; N-267 to A-281; A-268 to L-282; Q-269 to K-283; L-270 to L-284; and S-271 to L-285 of SEQ ID NO:3228.

The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to C-15; D-2 to L-16; D-3 to K-17; S-4 to K-18; F-5 to R-19; E-6 to E-20; R-7 to E-21; E-8 to M-22; Q-9 to K-23; S-10 to L-24; R-11 to K-25; L-12 to E-26; T-13 to C-27; S-14 to V-28; C-15 to S-29; L-16 to L-30; K-31 to L-31; K-18 to P-32; R-19 to R-33; E-20 to K-34; E-21 to E-35; M-22 to S-36; K-23 to P-37; L-24 to S-38; K-25 to V-39; E-36 to R-40; C-27 to S-41; V-28 to S-42; S-29 to K-43; L-30 to D-44; L-31 to G-45; P-32 to K-46; R-33 to L-47; K-34 to L-48; E-35 to A-49; S-36 to A-50; P-37 to T-51; S-38 to L-52; V-39 to L-53; R-40 to L-54; S-41 to A-55; S-42 to L-56; K-43 to L-57; D-44 to S-58; G-45 to C-59; K-46 to C-60; L-47 to L-61; L-48 to T-62; A-49 to V-63; A-50 to V-64; T-51 to S-65; L-52 to F-66; L-53 to G-67; L-54 to Q-68; A-55 to V-69; L-56 to A-70; L-57 to A-71; S-58 to L-72; C-59 to Q-73; C-60 to G-74; L-61 to D-75; T-62 to L-76; V-63 to A-77; V-64 to S-78; S-65 to L-79; F-66 to R-80; Y-67 to A-81; Q-68 to E-82; V-69 to L-83; A-70 to Q-84; A-71 to G-85; L-72 to H-86; Q-73 to H-87; G-74 to A-88; D-75 to E-89; L-76 to K-90; A-77 to L-91; S-78 to P-92; L-79 to A-93; R-80 to G-94; A-81 to A-95; E-82 to G-96; L-83 to A-97; Q-84 to P-98; G-85 to K-99; H-86 to A-100; H-87 to G-101; A-88 to L-102; E-89 to E-103; K-90 to E-104; L-91 to A-105; P-92 to P-106; A-93 to A-107; G-94 to V-108; A-95 to T-109; G-96 to A-110; A-97 to G-111; P-98 to L-112; K-99 to K-113; A-100 to L-114; G-101 to F-115; L-102 to E-116; E-103 to P-117; E-104 to P-118; A-105 to A-119; P-106 to P-120; A-107 to G-121; V-108 to E-122; T-109 to G-123; A-110 to N-124; G-111 to S-125; L-112 to S-126; K-113 to Q-127; L-114 to N-128; F-115 to S-129; E-116 to R-130; P-117 to N-131; P-118 to K-132; A-119 to R-133; P-120 to A-134; G-121 to V-135; E-122 to Q-136; G-123 to G-137; N-124 to P-138; S-125 to E-139; S-126 to E-140; Q-127 to T-141; N-128 to G-142; S-129 to S-143; R-130 to Y-144; N-131 to T-145; K-132 to F-146; R-133 to V-147; A-134 to P-148; V-135 to W-149; Q-136 to L-150; G-137 to L-151; P-138 to S-152; E-139 to F-153; E-140 to K-154; T-141 to R-155; G-142 to G-156; S-143 to S-157; Y-144 to A-158; T-145 to L-159; F-146 to E-160; V-147 to E-161; P-148 to K-162; W-149 to E-163; L-150 to N-164; L-151 to K-165; S-152 to L-166; F-153 to L-167; K-154 to V-168; R-155 to K-169; G-156 to E-170; S-157 to T-171;

A-158 to G-172; L-159 to Y-173; E-160 to F-174; E-161 to F-175; K-162 to L-176; E-163 to Y-177; N-164 to G-178; K-165 to Q-179; L-166 to V-180; L-167 to L-181; V-168 to Y-182; K-169 to T-183; E-170 to D-184; T-171 to K-185; G-172 to T-186; Y-173 to Y-187; F-174 to A-188; F-175 to M-189; L-176 to G-190; Y-177 to H-191; G-178 to L-192; Q-179 to L-193; V-180 to Q-194; L-181 to R-195; Y-182 to K-196; T-183 to K-197; D-184 to V-198; K-185 to H-199; T-186 to V-200; Y-187 to F-201; A-188 to G-202; M-189 to D-203; G-190 to L-204; H-191 to L-205; L-192 to S-206; L-193 to L-207; Q-194 to V-208; R-195 to T-209; K-196 to L-210; K-197 to F-211; V-198 to R-212; H-199 to C-213; V-200 to L-214; F-201 to Q-215; G-202 to N-216; D-203 to M-217; E-204 to P-218; L-205 to E-219; S-206 to T-220; L-207 to L-221; V-208 to P-222; T-209 to N-223; L-210 to N-224; F-211 to S-225; R-212 to C-226; C-213 to Y-227; L-214 to S-228; Q-215 to A-229; N-216 to G-230; M-217 to L-231; P-218 to A-232; E-219 to K-233; T-220 to L-234; L-221 to E-235; P-222 to E-236; N-223 to G-237; N-224 to D-238; S-225 to E-239; C-226 to L-240; Y-227 to Q-241; S-228 to L-242; A-229 to A-243; G-230 to L-244; L-231 to P-245; A-232 to R-246; K-233 to E-247; L-234 to N-248; E-235 to A-249; E-236 to Q-250; G-237 to L-251; D-238 to S-252; E-239 to L-253; L-240 to D-254; Q-241 to G-255; L-242 to D-256; A-243 to V-257; L-244 to T-258; P-245 to F-259; R-246 to F-260; E-247 to G-261; N-248 to A-262; A-249 to L-263; Q-250 to K-264; L-251 to L-265; and S-252 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to F-15; D-2 to C-16; E-3 to S-17; S-4 to E-18; A-5 to K-19; K-6 to G-20; T-7 to E-21; L-8 to D-22; P-9 to M-23; P-10 to K-24; P-11 to V-25; C-12 to G-26; L-13 to Y-27; C-14 to D-28; F-15 to P-29; C-16 to I-30; S-17 to T-31; E-18 to P-32; K-19 to Q-33; G-20 to K-34; E-21 to E-35; D-22 to E-36; M-23 to G-37; K-24 to A-38; V-25 to W-39; G-26 to F-40; Y-27 to G-41; D-28 to L-42; P-29 to C-43; I-30 to R-44; T-31 to D-45; P-32 to G-46; Q-33 to R-47; K-34 to L-48; E-35 to L-49; E-36 to A-50; G-37 to A-51; A-38 to T-52; W-39 to L-53; P-40 to L-54; G-41 to L-55; L-42 to A-56; C-43 to L-57; R-44 to L-58; D-45 to S-59; G-46 to S-60; R-47 to S-61; L-48 to F-62; L-49 to T-63; A-50 to A-64; A-51 to M-65; T-52 to S-66; L-53 to L-67; L-54 to Y-68; L-55 to Q-69; A-56 to L-70; L-57 to A-71; L-58 to A-72; S-59 to L-73; S-60 to Q-74; S-61 to A-75; F-62 to D-76; T-63 to L-77; A-64 to M-78; M-65 to N-79; S-66 to L-80; L-67 to R-81; Y-68 to M-82; Q-69 to E-83; L-70 to L-84; A-71 to Q-85; A-72 to S-86; L-73 to Y-87; Q-74 to R-88; A-75 to G-89; D-76 to S-90; L-77 to A-91; M-78 to T-92; N-79 to P-93; L-80 to A-94; R-81 to A-95; M-82 to A-96; E-83 to G-97; L-84 to A-98; Q-85 to P-99; S-86 to E-100; Y-87 to L-101; R-88 to T-102; G-89 to A-103; S-90 to G-104; A-91 to V-105; T-92 to K-106; P-93 to L-107; A-94 to L-108; A-95 to T-109; A-96 to P-110; G-97 to A-111; A-98 to A-112; P-99 to P-113; E-100 to R-114; L-101 to P-115; T-102 to H-116; A-103 to N-117; G-104 to S-118; V-105 to S-119; K-106 to R-120; L-107 to G-121; L-108 to H-122; T-109 to R-123; P-110 to N-124; A-111 to R-125; A-112 to R-126; P-113 to A-127; R-114 to F-128; P-115 to Q-129;



H-116 to G-130; N-117 to P-131; S-118 to E-132; S-119 to E-133; R-120 to T-134; G-121 to E-135; H-122 to Q-136; R-123 to D-137; N-124 to V-138; R-125 to D-139; R-126 to L-140; A-127 to S-141; F-128 to A-142; Q-129 to P-143; G-130 to P-144; P-131 to A-145; E-132 to P-146; E-133 to C-147; T-134 to L-148; A-145 to P-149; Q-136 to G-150; D-137 to C-151; V-138 to R-152; D-139 to H-153; L-140 to S-154; S-141 to Q-155; A-142 to H-156; P-143 to D-157; P-144 to D-158; A-145 to N-159; P-146 to G-160; C-147 to M-161; L-148 to N-162; P-149 to L-163; G-150 to R-164; C-151 to N-165; R-152 to L-166; H-153 to I-167; S-154 to Q-168; Q-155 to D-169; H-156 to C-170; D-157 to L-171; D-158 to Q-172; N-159 to L-173; G-160 to I-174; M-161 to A-175; N-162 to D-176; L-163 to S-177; R-164 to D-178; N-165 to T-179; I-166 to P-180; I-167 to A-181; Q-168 to L-182; D-169 to E-183; C-170 to E-184; L-171 to K-185; Q-172 to E-186; L-173 to N-187; I-174 to K-188; A-175 to I-189; D-176 to V-190; S-177 to P-191; D-178 to R-192; T-179 to Q-193; P-180 to T-194; A-181 to G-195; L-182 to Y-196; E-183 to F-197; E-184 to F-198; K-185 to I-199; E-186 to Y-200; N-187 to S-201; K-188 to Q-202; I-189 to V-203; V-190 to L-204; V-191 to Y-205; R-192 to T-206; Q-193 to D-207; T-194 to P-208; G-195 to I-209; Y-196 to F-210; F-197 to A-211; F-198 to M-212; I-199 to G-213; Y-200 to H-214; S-201 to V-215; Q-202 to I-216; V-203 to Q-217; L-204 to R-218; Y-205 to K-219; T-206 to K-220; D-207 to V-221; P-208 to H-222; I-209 to V-223; F-210 to F-224; A-211 to G-225; M-212 to D-226; G-213 to E-227; I-214 to L-228; V-215 to S-229; I-216 to L-230; Q-217 to V-231; R-218 to T-232; K-219 to L-233; K-220 to F-234; V-221 to R-235; H-222 to C-236; V-223 to I-237; F-224 to Q-238; G-225 to N-239; D-226 to M-240; E-227 to P-241; L-228 to K-242; S-229 to T-243; L-230 to L-244; V-231 to P-245; T-232 to N-246; L-233 to N-247; F-234 to S-248; R-235 to C-249; C-236 to Y-250; I-237 to S-251; Q-238 to A-252; N-239 to G-253; M-240 to I-254; P-241 to A-255; K-242 to R-256; T-243 to L-257; L-244 to E-258; P-245 to E-259; N-246 to G-260; N-247 to D-261; S-248 to E-262; C-249 to I-263; Y-250 to Q-264; S-251 to L-265; A-252 to A-266; G-253 to I-267; I-254 to P-268; A-255 to R-269; P-256 to E-270; L-257 to N-271; E-258 to A-272; E-259 to Q-273; G-260 to I-274; D-261 to S-275; E-262 to R-276; I-263 to N-277; Q-264 to G-278; L-265 to D-279; A-266 to D-280; I-267 to T-281; P-268 to F-282; R-269 to F-283; E-270 to A-284; N-271 to A-285; A-272 to L-286; Q-273 to K-287; I-274 to L-288; and S-275 to L-289 of SEQ ID NO.38. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

It will be recognized by one of ordinary skill in the art that some amino acid sequences of the B Lymphocyte Stimulator polypeptides can be varied without significant effect of the structure or function of the polypeptide. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the polypeptide which determine activity.

Thus, the invention further includes antibodies that bind variations of B Lymphocyte Stimulator polypeptides which show B Lymphocyte Stimulator polypeptide functional activity (e.g., biological activity) or which include regions of B Lymphocyte Stimulator polypeptide such as the polypeptide fragments described herein. Such mutants include deletions, insertions, inversions, repeats, and type substitutions selected according to general rules known in the art so as

have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science* 247:1306-1310 (1990), wherein the authors indicate that there are two main approaches for studying the tolerance of an amino acid sequence to change. The first method relies on the process of evolution, in which mutations are either accepted or rejected by natural selection. The second approach uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene and selections or screens to identify sequences that maintain functionality.

As the authors state, these studies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at a certain position of the protein. For example, most buried amino acid residues require non-polar side chains, whereas few features of surface side chains are generally conserved. Other such phenotypically silent substitutions are described in Bowie, J. U. et al., supra, and the references cited therein. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the aromatic residues Phe, Tyr.

Thus, antibodies of the present invention may bind fragments, derivatives or analogs of the polypeptide of SEQ ID NO.3228, or that encoded by the deposited cDNA plasmid, such as (i) polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) polypeptides in which one or more of the amino acid residues includes a substituent group, or (iii) polypeptides in which the extracellular domain of the polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) polypeptides in which the additional amino acids are fused to the extracellular domain of the polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the extracellular domain of the polypeptide or a propeptide sequence.

Antibodies of the present invention may bind fragments, derivatives or analogs of the polypeptide of SEQ ID NO.3229, or that encoded by the deposited cDNA plasmid, such as (i) polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) polypeptides in which one or more of the amino acid residues includes a substituent group, or (iii) polypeptides in which the extracellular domain of the polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) polypeptides in which the additional amino acids are fused to the extracellular domain of the polypeptide, such as, a soluble biologically active fragment of another TNF ligand family member (e.g., CD40 Ligand), an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the extra-

cellular domain of the polypeptide or a propeptide sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

Thus, the antibodies of the invention may bind B Lymphocyte Stimulator polypeptides that include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation. As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein (see Table 13).

TABLE 13

Conservative Amino Acid Substitutions.	
Aromatic	Phenylalanine
	Tryptophan
Hydrophobic	Tyrosine
	Leucine
Polar	Isoleucine
	Valine
Basic	Glutamine
	Asparagine
Acidic	Arginine
	Lysine
Small	Histidine
	Aspartic Acid
	Glutamic Acid
	Serine
	Alanine
	Threonine
	Methionine
	Glycine

In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a B Lymphocyte Stimulator polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 50 conservative amino acid substitutions, even more preferably, not more than 40 conservative amino acid substitutions, still more preferably, not more than 30 conservative amino acid substitutions, and still even more preferably, not more than 20 conservative amino acid substitutions. In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a B Lymphocyte Stimulator polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 conservative amino acid substitutions.

For example, site directed changes at the amino acid level of B Lymphocyte Stimulator can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind B Lymphocyte Stimulator amino acid sequences containing conservative substitution mutations of the polypeptide of SEQ ID NO:3228 including: M1 replaced with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, T, M, or V; L16 replaced with A, G, I, S, T, M, or V; K17 replaced with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24

replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; I30 replaced with A, G, L, S, T, M, or V; L31 replaced with A, G, I, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with A, G, I, L, T, M, or V; V39 replaced with A, G, I, L, S, T, or M; R40 replaced with H, or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, I, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, I, L, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55 replaced with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaced with A, G, I, S, T, M, or V; R80 replaced with H, or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83 replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S, T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G, I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H, or R; L91 replaced with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; A97 replaced with G, I, L, S, T, M, or V; K99 replaced with H, or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, or M; T109 replaced with A, G, I, L, S, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, S, T, M, or V; K113 replaced with H, or R; I114 replaced with A, G, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaced with G, I, L, S, T, M, or V; G121 replaced with A, I, L, S, T, M, or V; E122 replaced with D; G123 replaced with A, I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, T, M, or V; S126 replaced with A, G, I, L, T, M, or V; Q127 replaced with N; N128 replaced with Q; S129 replaced with A, G, I, L, T, M, or V; R130 replaced with H, or K; N131 replaced with Q; K132 replaced with H, or R; R133 replaced with H, or K; A134 replaced with G, I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, or M; Q136 replaced with N; G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D; T141 replaced with A, G, I, L, S, M, or V; V142 replaced with A, G, I, L, S, T, or M; T143 replaced with A, G, I, L, S, M, or V; Q144 replaced with N; D145 replaced with E; L147 replaced with A, G, I,

S, T, M, or V; Q148 replaced with N; L149 replaced with A, G, I, S, T, M, or V; I150 replaced with A, G, I, S, T, M, or V; A151 replaced with G, I, L, S, T, M, or V; D152 replaced with E; S153 replaced with A, G, I, L, T, M, or V; E154 replaced with D; T155 replaced with A, G, I, L, S, T, M, or V; T157 replaced with A, G, I, L, S, M, or V; I158 replaced with A, G, I, S, T, M, or V; Q159 replaced with N; K160 replaced with H, or R; G161 replaced with A, I, L, S, T, M, or V; S162 replaced with A, G, I, L, T, M, or V; Y163 replaced with F, or W; T164 replaced with A, G, I, L, S, M, or V; F165 replaced with W, or Y; V166 replaced with A, G, I, L, S, T, or M; W168 replaced with F, or Y; L169 replaced with A, G, I, S, T, M, or V; L170 replaced with A, G, I, S, T, M, or V; S171 replaced with A, G, I, L, T, M, or V; F172 replaced with W, or Y; K173 replaced with H, or R; R174 replaced with H, or K; G175 replaced with A, I, L, S, T, M, or V; S176 replaced with A, G, I, L, T, M, or V; A177 replaced with G, I, L, S, T, M, or V; L178 replaced with A, G, I, S, T, M, or V; E179 replaced with D; E180 replaced with D; K181 replaced with H, or R; E182 replaced with D; N183 replaced with Q; K184 replaced with H, or R; I185 replaced with A, G, I, S, T, M, or V; L186 replaced with A, G, I, S, T, M, or V; V187 replaced with A, G, I, L, S, T, or M; K188 replaced with H, or R; E189 replaced with D; T190 replaced with A, G, I, L, S, M, or V; G191 replaced with A, I, L, S, T, M, or V; Y192 replaced with F, or W; F193 replaced with W, or Y; F194 replaced with W, or Y; I195 replaced with A, G, I, S, T, M, or V; Y196 replaced with F, or W; G197 replaced with A, I, L, S, T, M, or V; Q198 replaced with N; V199 replaced with A, G, I, L, S, T, or M; L200 replaced with A, G, I, S, T, M, or V; Y201 replaced with F, or W; T202 replaced with A, G, I, L, S, M, or V; D203 replaced with E; K204 replaced with H, or R; T205 replaced with A, G, I, L, S, M, or V; Y206 replaced with F, or W; A207 replaced with G, I, L, S, T, M, or V; M208 replaced with A, G, I, L, S, T, or V; G209 replaced with A, I, L, S, T, M, or V; H210 replaced with K, or R; L211 replaced with A, G, I, S, T, M, or V; I212 replaced with A, G, I, L, S, T, M, or V; Q213 replaced with N; R214 replaced with H, or K; K215 replaced with H, or R; K216 replaced with H, or R; V217 replaced with A, G, I, L, S, T, or M; H218 replaced with K, or R; V219 replaced with A, G, I, L, S, T, or M; F220 replaced with W, or Y; G221 replaced with A, I, L, S, T, M, or V; D222 replaced with E; E223 replaced with D; L224 replaced with A, G, I, S, T, M, or V; S225 replaced with A, G, I, L, T, M, or V; L226 replaced with A, G, I, S, T, M, or V; V227 replaced with A, G, I, L, S, T, or M; T228 replaced with A, G, I, L, S, M, or V; L229 replaced with A, G, I, L, S, T, M, or V; F230 replaced with W, or Y; R231 replaced with H, or K; I233 replaced with A, G, I, L, S, T, M, or V; Q234 replaced with N; N235 replaced with Q; M236 replaced with A, G, I, L, S, T, or V; E238 replaced with D; T239 replaced with A, G, I, L, S, M, or V; L240 replaced with A, G, I, S, T, M, or V; N242 replaced with Q; N243 replaced with Q; S244 replaced with A, G, I, L, T, M, or V; Y246 replaced with F, or W; S247 replaced with A, G, I, L, T, M, or V; A248 replaced with G, I, L, S, T, M, or V; G249 replaced with A, I, L, S, T, M, or V; I250 replaced with A, G, I, L, S, T, M, or V; A251 replaced with G, I, L, S, T, M, or V; K252 replaced with H, or R; L253 replaced with A, G, I, S, T, M, or V; E254 replaced with D; E255 replaced with D; G256 replaced with A, I, L, S, T, M, or V; V257 replaced with E; E258 replaced with D; L259 replaced with A, G, I, S, T, M, or V; Q260 replaced with N; L261 replaced with A, G, I, S, T, M, or V; A262 replaced with G, I, L, S, T, M, or V; I263 replaced with A, G, I, L, S, T, M, or V; R265 replaced with H, or K; E266 replaced with D; N267 replaced with Q; A268 replaced with G, I, L, S, T,

M, or V; Q269 replaced with N; I270 replaced with A, G, I, S, T, M, or V; S271 replaced with A, G, I, L, T, M, or V; L272 replaced with A, G, I, S, T, M, or V; D273 replaced with E; G274 replaced with A, I, L, S, T, M, or V; D275 replaced with E; V276 replaced with A, G, I, L, S, T, or M; T277 replaced with A, G, I, L, S, M, or V; F278 replaced with W, or Y; F279 replaced with W, or Y; G280 replaced with A, I, L, S, T, M, or V; A281 replaced with G, I, L, S, T, M, or V; L282 replaced with A, G, I, S, T, M, or V; K283 replaced with H, or R; L284 replaced with A, G, I, S, T, M, or V; and/or L285 replaced with A, G, I, S, T, M, or V.

In another embodiment, site directed changes at the amino acid level of B Lymphocyte Stimulator can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind B Lymphocyte Stimulator amino acid sequences containing conservative substitution mutations of the polypeptide of SEQ ID NO:3229 including: M1 replaced with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, T, M, or V; L16 replaced with A, G, I, S, T, M, or V; K17 replaced with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24 replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; I30 replaced with A, G, I, L, S, T, M, or V; L31 replaced with A, G, I, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with A, G, I, L, T, M, or V; V39 replaced with A, G, I, L, S, T, or M; R40 replaced with H, or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, I, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, I, L, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55 replaced with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaced with A, G, I, S, T, M, or V; R80 replaced with H, or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83 replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S, T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G, I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H, or R; L91 replaced

with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; A97 replaced with G, I, L, S, T, M, or V; K99 replaced with H, or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, L, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, M, or V; T109 replaced with A, G, I, L, S, T, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, L, S, T, M, or V; K113 replaced with H, or R; I114 replaced with A, G, I, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaced with G, I, L, S, T, M, or V; G121 replaced with A, I, L, S, T, M, or V; E122 replaced with D; G123 replaced with A, I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, S, T, M, or V; S126 replaced with A, G, I, L, S, T, M, or V; Q127 replaced with N; N128 replaced with Q; S129 replaced with A, G, I, L, S, T, M, or V; R130 replaced with H, or K; N131 replaced with Q; K132 replaced with H, or R; R133 replaced with H, or K; A134 replaced with G, I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, M, or V; Q136 replaced with N; G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D; T141 replaced with A, G, I, L, S, T, M, or V; G142 replaced with A, I, L, S, T, M, or V; S143 replaced with A, G, I, L, S, T, M, or V; Y144 replaced with F, or W; T145 replaced with A, G, I, L, S, T, M, or V; F146 replaced with W, or Y; V147 replaced with A, G, I, L, S, T, M, or V; W149 replaced with F, or Y; L150 replaced with A, G, I, L, S, T, M, or V; L151 replaced with A, G, I, L, S, T, M, or V; S152 replaced with A, G, I, L, S, T, M, or V; F153 replaced with W, or Y; K154 replaced with H, or R; R155 replaced with H, or K; G156 replaced with A, I, L, S, T, M, or V; S157 replaced with A, G, I, L, S, T, M, or V; A158 replaced with G, I, L, S, T, M, or V; L159 replaced with A, G, I, L, S, T, M, or V; E160 replaced with D; E161 replaced with D; K162 replaced with H, or R; E163 replaced with D; N164 replaced with Q; K165 replaced with H, or R; I166 replaced with A, G, I, L, S, T, M, or V; L167 replaced with A, G, I, L, S, T, M, or V; V168 replaced with A, G, I, L, S, T, M, or V; K169 replaced with H, or R; E170 replaced with D; T171 replaced with A, G, I, L, S, T, M, or V; G172 replaced with A, I, L, S, T, M, or V; Y173 replaced with F, or W; F174 replaced with W, or Y; F175 replaced with W, or Y; I176 replaced with A, G, I, L, S, T, M, or V; Y177 replaced with F, or W; G178 replaced with A, I, L, S, T, M, or V; Q179 replaced with N; V180 replaced with A, G, I, L, S, T, M, or V; L181 replaced with A, G, I, L, S, T, M, or V; Y182 replaced with F, or W; T183 replaced with A, G, I, L, S, T, M, or V; D184 replaced with E; K185 replaced with H, or R; T186 replaced with A, G, I, L, S, T, M, or V; Y187 replaced with F, or W; A188 replaced with G, I, L, S, T, M, or V; M189 replaced with A, G, I, L, S, T, M, or V; G190 replaced with A, I, L, S, T, M, or V; H191 replaced with K, or R; L192 replaced with A, G, I, L, S, T, M, or V; I193 replaced with A, G, I, L, S, T, M, or V; Q194 replaced with N; R195 replaced with H, or K; K196 replaced with H, or R; K197 replaced with H, or R; V198 replaced with A, G, I, L, S, T, M, or V; H199 replaced with K, or R; V200 replaced with A, G, I, L, S, T, M, or V; F201 replaced with W, or Y; G202 replaced with A, I, L, S, T, M, or V; D203 replaced with E; E204 replaced with D; L205 replaced with A, G, I, L, S, T, M, or V; S206 replaced with A, G, I, L, S, T, M, or V; L207 replaced with A, G, I, L, S, T, M, or V; V208 replaced with A, G, I, L, S, T, M, or V; T209 replaced with A, G, I, L, S, T, M, or V; L210 replaced with A, G, I, L, S, T, M, or V; F211 replaced

with W, or Y; R212 replaced with H, or K; I214 replaced with A, G, I, L, S, T, M, or V; Q215 replaced with N; N216 replaced with Q; M217 replaced with A, G, I, L, S, T, M, or V; E219 replaced with D; T220 replaced with A, G, I, L, S, T, M, or V; L221 replaced with A, G, I, L, S, T, M, or V; N223 replaced with Q; N224 replaced with Q; S225 replaced with A, G, I, L, S, T, M, or V; Y227 replaced with F, or W; S228 replaced with A, G, I, L, S, T, M, or V; A229 replaced with G, I, L, S, T, M, or V; G230 replaced with A, I, L, S, T, M, or V; V231 replaced with A, G, I, L, S, T, M, or V; A232 replaced with G, I, L, S, T, M, or V; K233 replaced with H, or R; L234 replaced with A, G, I, L, S, T, M, or V; E235 replaced with D; E236 replaced with D; G237 replaced with A, I, L, S, T, M, or V; D238 replaced with E; E239 replaced with D; L240 replaced with A, G, I, L, S, T, M, or V; Q241 replaced with N; L242 replaced with A, G, I, L, S, T, M, or V; A243 replaced with G, I, L, S, T, M, or V; L244 replaced with A, G, I, L, S, T, M, or V; R246 replaced with H, or K; E247 replaced with D; N248 replaced with Q; A249 replaced with G, I, L, S, T, M, or V; Q250 replaced with N; I251 replaced with A, G, I, L, S, T, M, or V; S252 replaced with A, G, I, L, S, T, M, or V; L253 replaced with A, G, I, L, S, T, M, or V; D254 replaced with E; G255 replaced with A, I, L, S, T, M, or V; D256 replaced with E; V257 replaced with A, G, I, L, S, T, M, or V; T258 replaced with A, G, I, L, S, T, M, or V; F259 replaced with W, or Y; F260 replaced with W, or Y; G261 replaced with A, I, L, S, T, M, or V; A262 replaced with G, I, L, S, T, M, or V; L263 replaced with A, G, I, L, S, T, M, or V; K264 replaced with H, or R; L265 replaced with A, G, I, L, S, T, M, or V; and/or L266 replaced with A, G, I, L, S, T, M, or V.

In another embodiment, site directed changes at the amino acid level of B Lymphocyte Stimulator can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind B Lymphocyte Stimulator amino acid sequences containing conservative substitution mutations of the polypeptide of any one of SEQ ID NOS:3230-3237.

Amino acids in the B Lymphocyte Stimulator polypeptides that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for functional activity, such as ligand binding and the ability to stimulate lymphocyte (e.g., B cell) as, for example, proliferation, differentiation, and/or activation. Accordingly, antibodies of the present invention may bind amino acids in the B Lymphocyte Stimulator polypeptides that are essential for function. In preferred embodiments, antibodies of the present invention bind amino acids in the B Lymphocyte Stimulator polypeptides that are essential for function and inhibit B Lymphocyte Stimulator polypeptide function. In other preferred embodiments, antibodies of the present invention bind amino acids in the B Lymphocyte Stimulator polypeptides that are essential for function and enhance B Lymphocyte Stimulator polypeptide function.

Of special interest are substitutions of charged amino acids with other charged or neutral amino acids which may produce proteins with highly desirable improved characteristics, such as less aggregation. Aggregation may not only reduce activity but also be problematic when preparing pharmaceutical formulations, because aggregates can be immunogenic (Pinckard et al., *Clin. Exp. Immunol.* 2:331-340 (1967); Robbins et al., *Diabetes* 36: 838-845 (1987); Cleland et al., *Crit. Rev. Therapeutic Drug Carrier Systems* 10:307-377 (1993)).

In another embodiment, the invention provides for antibodies that bind polypeptides having amino acid sequences containing non-conservative substitutions of the amino acid sequence provided in SEQ ID NO:3228. For example, non-conservative substitutions of the B Lymphocyte Stimulator protein sequence provided in SEQ ID NO:3228 include: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D2 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D3 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S4 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T5 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E6 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R7 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E8 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q9 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R11 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C15 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K17 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K18 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R19 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E20 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E21 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K23 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K25 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E26 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C27 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V28 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S29 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I30 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L31 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C32 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R33 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K34 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E35 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S36 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P37 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S38 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V39 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R40 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S41 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S42 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K43 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D44 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G45 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K46 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L47 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A49 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A50 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T51 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L52 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A55 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L56 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L57 replaced with D, E, H, K, R, N, Q, F, W,

Y, P, or C; S58 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C59 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C60 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L61 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T62 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V63 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V64 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S65 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P66 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y67 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q68 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V69 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A70 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A71 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L72 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q73 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G74 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D75 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L76 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A77 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S78 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L79 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R80 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A81 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E82 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L83 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q84 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G85 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H86 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H87 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A88 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E89 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K90 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L91 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P92 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A93 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G94 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A95 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G96 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A97 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P98 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K99 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A100 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G101 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E103 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E104 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A105 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P106 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A107 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T109 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A110 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G111 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L112 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K113 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I114 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E116 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P117 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P118 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A119 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P120 replaced with D, E, H, K,



Q, F, W, Y, or C; N242 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N243 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S244 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; C245 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Y246 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S247 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A248 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G249 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I250 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A251 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K252 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L253 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E254 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E255 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G256 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D257 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E258 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L259 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q260 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L261 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A262 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I263 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P264 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R265 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E266 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N267 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; D268 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q269 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I270 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S271 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L272 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D273 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G274 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D275 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V276 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T277 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F278 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F279 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G280 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A281 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L282 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K283 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L284 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; and/or L285 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C.

In an additional embodiment, antibodies of the present invention bind B Lymphocyte Stimulator polypeptides comprising, or alternatively consisting of, a B Lymphocyte Stimulator amino acid sequence in which more than one amino acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 and 50) is replaced with the substituted amino acids as described above (either conservative or nonconservative).

In another embodiment of the invention, antibodies of the present invention bind B Lymphocyte Stimulator polypeptides with non-conservative substitutions of the sequence provided in SEQ ID NO:3229 including: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D2 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D3 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S4 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T5 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E6 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R7 replaced with D, E, A, G, I, L, S, T, M, V, N,

Q, F, W, Y, P, or C; E8 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q9 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R11 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C15 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K17 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K18 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R19 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E20 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E21 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K23 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K25 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E26 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C27 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V28 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S29 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I30 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L31 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P32 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R33 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K34 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E35 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S36 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P37 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V38 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R40 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S41 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S42 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K43 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D44 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G45 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K46 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L47 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A49 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T51 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L52 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A55 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L56 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L57 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S58 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C59 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C60 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L61 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T62 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V63 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V64 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S65 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P66 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y67 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q68 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V69 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A70





C; I193 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q194 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R195 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K196 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K197 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V198 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I199 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V200 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F201 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G202 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D203 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E204 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L205 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S206 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L207 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V208 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T209 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L210 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F211 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R212 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C213 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I214 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q215 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N216 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; M217 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P218 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E219 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T220 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L221 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P222 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N223 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N224 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S225 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C226 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Y227 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S228 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A229 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G230 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I231 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A232 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K233 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L234 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E235 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E236 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G237 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D238 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E239 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L240 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q241 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L242 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A243 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I244 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P245 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R246 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E247 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N248 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A249 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q250 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I251 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S252 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L253

replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D254 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G255 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D256 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V257 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T258 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F259 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F260 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G261 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A262 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L263 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K264 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L265 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; and/or L266 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C.

In another embodiment, site directed changes at the amino acid level of B Lymphocyte Stimulator can be made by replacing a particular amino acid with a non-conservative substitution. Antibodies of the present invention may bind B Lymphocyte Stimulator amino acid sequences containing non-conservative substitution mutations of the polypeptide of any one of SEQ ID NOS:3230-3237.

In an additional embodiment, antibodies of the present invention bind B Lymphocyte Stimulator polypeptides comprising, or alternatively consisting of, a B Lymphocyte Stimulator amino acid sequence in which more than one amino acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 and 50) is replaced with the substituted amino acids as described above (either conservative or nonconservative).

Replacement of amino acids can also change the selectivity of the binding of a ligand to cell surface receptors. For example, Ostade et al., *Nature* 361:266-268 (1993) describes certain mutations resulting in selective binding of TNF-alpha to only one of the two known types of TNF receptors. Since B Lymphocyte Stimulator is a member of the TNF polypeptide family, mutations similar to those in TNF-alpha are likely to have similar effects in B Lymphocyte Stimulator polypeptides.

Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith et al., *J. Mol. Biol.* 224:899-904 (1992) and de Vos et al., *Science* 255:306-312 (1992)).

Since B Lymphocyte Stimulator is a member of the TNF-related protein family, mutations may be made in sequences encoding amino acids in the TNF conserved domain, e.g., in positions Gly-191 through Leu-284 of SEQ ID NO:3228 or in positions Gly-172 through Leu-265 of SEQ ID NO:3229, may modulate rather than completely eliminate functional activities (e.g., biological activities) of B Lymphocyte Stimulator polypeptides or fragments or variants thereof. Accordingly, antibodies of the present invention may bind B Lymphocyte Stimulator polypeptides that have mutations in the TNF conserved domain. In preferred embodiments, antibodies of the present invention may bind B Lymphocyte Stimulator polypeptides that have mutations in the TNF conserved domain and act as antagonists of B Lymphocyte Stimulator. In other preferred embodiments, antibodies of the present invention may bind B Lymphocyte Stimulator polypeptides that have mutations in the TNF conserved domain and act as agonists of B Lymphocyte Stimulator.

Recombinant DNA technology known to those skilled in the art (see, for instance, DNA shuffling supra) can be used to create novel mutant proteins or muteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g.,

enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions.

Thus, the invention also encompasses antibodies that bind B Lymphocyte Stimulator derivatives and analogs that have one or more amino acid residues deleted, added, or substituted to generate B Lymphocyte Stimulator polypeptides, e.g., that are better suited for expression, scale up, etc., in the host cells. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges; N-linked glycosylation sites can be altered or eliminated to achieve, for example, expression of a homogeneous product that is more easily recovered and purified from yeast hosts which are known to hyperglycosylate N-linked sites. To this end, a variety of amino acid substitutions at one or both of the first or third amino acid positions on any one or more of the glycosylation recognition sequences in the B Lymphocyte Stimulator polypeptides of the invention, and/or an amino acid deletion at the second position of any one or more such recognition sequences will prevent glycosylation of the B Lymphocyte Stimulator at the modified tripeptide sequence (see, e.g., Miyajima et al., EMBO J 5(6):1193-1197). By way of non-limiting example, mutation of the serine at position 244 to alanine either singly or in combination with mutation of the asparagine at position 242 to glutamine abolishes glycosylation of the mature soluble form of B Lymphocyte Stimulator (e.g., amino acids 134-285 of SEQ ID NO:3228) when expressed in the yeast *Pichia pastoris*. A mutant B Lymphocyte Stimulator polypeptide in which only the asparagine at position 242 is mutated to glutamine, is still glycosylated when expressed in *Pichia pastoris*. In this mutant, the glycosylation event may be due to the activation or unmasking of an O-linked glycosylation site at serine 244. Similar mutations affecting glycosylation could also be made in the B Lymphocyte Stimulator polypeptide of SEQ ID NO:3229, i.e., asparagine-223 to glutamine and/or serine-224 to alanine of SEQ ID NO:3229. Additionally, one or more of the amino acid residues of the polypeptides of the invention (e.g., arginine and lysine residues) may be deleted or substituted with another residue to eliminate undesired processing by proteases such as, for example, furins or kexins. One possible result of such a mutation is that B Lymphocyte Stimulator polypeptide of the invention is not cleaved and released from the cell surface. Accordingly, antibodies of the invention may bind B Lymphocyte Stimulator derivatives and analogs that have one or more amino acid residues deleted, added, or substituted. In other embodiments, antibodies of the invention may bind B Lymphocyte Stimulator derivatives, variants or analogs that are unable to be cleaved from the cell surface.

In a specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Lys-132 and/or Arg-133 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, to prevent or diminish release of the soluble form of B Lymphocyte Stimulator from cells expressing B Lymphocyte Stimulator. In a more specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Lys-132 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to Ala-132. In another, nonexclusive specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Arg-133 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to Ala-133. These mutated proteins,

and/or have uses such as, for example, in ex vivo therapy or gene therapy, to engineer cells expressing a B Lymphocyte Stimulator polypeptide that is retained on the surface of the engineered cells.

In a specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Cys-146 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant B Lymphocyte Stimulator polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Cys-146 is replaced with a serine amino acid residue.

In another specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Cys-232 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant B Lymphocyte Stimulator polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Cys-232 is replaced with a serine amino acid residue. Polypeptides encoding these polypeptides are also encompassed by the invention.

In yet another specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Cys-245 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant B Lymphocyte Stimulator polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Cys-245 is replaced with a serine amino acid residue. Polypeptides encoding these polypeptides are also encompassed by the invention.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of the B Lymphocyte Stimulator polypeptides can be substantially purified by the one-step method described in Smith and Johnson, *Gene* 67:31-40 (1988).

The antibodies of the present invention bind B Lymphocyte Stimulator polypeptides including the complete polypeptide encoded by the deposited cDNA (ATCC™ Deposit No. 97768) including the intracellular, transmembrane and extracellular domains of the polypeptide encoded by the deposited cDNA, the mature soluble polypeptide encoded by the deposited cDNA, the extracellular domain minus the intracellular and transmembrane domains of the protein, the complete polypeptide of SEQ ID NO:3228, the mature soluble polypeptide of SEQ ID NO:3228, e.g., amino acids 134-285 of SEQ ID NO:3228, the extracellular domain of SEQ ID NO:3228, amino acid residues 73-285 of SEQ ID NO:3228 minus the intracellular and transmembrane domains, as well as polypeptides which have at least 80%, 85%, 90% similarity, more preferably at least 95% similarity, and still more preferably at least 96%, 97%, 98% or 99% similarity to those described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The antibodies of the present invention bind B Lymphocyte Stimulator polypeptides including the complete polypeptide encoded by the deposited cDNA including the intracellular, transmembrane and extracellular domains of

the polypeptide encoded by the deposited cDNA (ATCC™ Deposit No. 203518), the mature soluble polypeptide encoded by the deposited cDNA, the extracellular domain minus the intracellular and transmembrane domains of the protein, the complete polypeptide of SEQ ID NO:3229, the mature soluble of SEQ ID NO:3229, e.g., amino acid residues 134-266 of SEQ ID NO:3229, the extracellular domain of SEQ ID NO:3229, e.g., amino acid residues 73-266 of SEQ ID NO:3229 minus the intracellular and transmembrane domains, as well as polypeptides which have at least 80%, 85%, 90% similarity, more preferably at least 95% similarity, and still more preferably at least 96%, 97%, 98% or 99% similarity to those described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Further antibodies of the present invention bind polypeptides including polypeptides at least 80%, or at least 85% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptide encoded by the deposited cDNA (ATCC™ Deposit No. 97768) or to the polypeptide of SEQ ID NO:3228, and also include antibodies that bind portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

Further antibodies of the present invention bind polypeptides including polypeptides at least 80%, or at least 85% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptide encoded by the deposited cDNA (ATCC™ Deposit No. 203518) or to the polypeptide of SEQ ID NO:3229, and also include antibodies that bind portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids. Polynucleotides encoding these polypeptides are also encompassed by the invention.

By "similarity" for two polypeptides is intended a similarity score produced by comparing the amino acid sequences of the two polypeptides using the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, Wis. 53711) and the default settings for determining similarity. Bestfit uses the local homology algorithm of Smith and Waterman (Advances in Applied Mathematics 2:482-489, 1981) to find the best segment of similarity between two sequences.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a reference amino acid sequence of a B Lymphocyte Stimulator polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid of the B Lymphocyte Stimulator polypeptide. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to 5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of SEQ ID

NO:3228, the amino acid sequence encoded by the deposited cDNA clone HNEDU15 (ATCC™ Accession No. 97768), or fragments thereof, or, for instance, to the amino acid sequence of SEQ ID NO:3229, the amino acid sequence encoded by the deposited cDNA clone HDPMS2 (ATCC™ Accession No. 203518), or fragments thereof, can be determined conventionally using known computer programs such as the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, Wis. 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

In a specific embodiment, the identity between a reference (query) sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. A determination of whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of this embodiment. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence. For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue

query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

#### Antibodies that Immunospecifically Bind B Lymphocyte Stimulator Polypeptides

The present invention also encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator polypeptides, which antibodies comprise, or alternatively consist of, all or a portion of a heavy and/or light chain variable domain of the scFvs referred to in Table 1.

The present invention also encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor function in an animal, preferably a mammal, and most preferably a human, comprising using antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator. Diseases and disorders which can be detected, diagnosed or prognosed with the antibodies of the invention include, but are not limited to, immune disorders (e.g., lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (e.g., asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (e.g., AIDS), and proliferative disorders (e.g., leukemia, carcinoma, and lymphoma).

The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor function in an animal, preferably a mammal, and most preferably a human, comprising administering to said animal an effective amount of one or more antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator. Diseases and disorders which can be prevented, treated or inhibited by administering an effective amount of one or more antibodies or molecules of the invention include, but are not limited to, immune disorders (e.g., lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (e.g., asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (e.g., AIDS), and proliferative disorders (e.g., leukemia, carcinoma, and lymphoma).

#### Anti-B Lymphocyte Stimulator Antibodies

The antibodies of the present invention were discovered, in part, using phage display technology. Single chain antibody molecules ("scFvs") displayed on the surface of phage particles were screened to identify those scFvs that immunospecifically bind to B Lymphocyte Stimulator, including the membrane-bound form and soluble form of B Lymphocyte Stimulator. The present invention encompasses the scFvs and portions thereof that were identified to immunospecifically bind to B Lymphocyte Stimulator, including

scFvs that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, scFvs that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, and scFvs that immunospecifically bind to both the soluble form and membrane-bound form of B Lymphocyte Stimulator. In particular, the present invention encompasses scFvs comprising, or alternatively consisting of, the amino acid sequence of SEQ ID NOS: 1-2128, as referred to in Table 1. Preferably, the scFvs of the present invention comprise, or alternatively consist of, the amino acid sequence of SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908. The scFvs include scFvs that bind to soluble B Lymphocyte Stimulator (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1563-1880), scFvs that bind to the membrane-bound form of B Lymphocyte Stimulator (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1881-2128), and scFvs that bind to both the soluble form and the membrane-bound form of B Lymphocyte Stimulator (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1-1562). Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

In one embodiment of the present invention, scFvs that immunospecifically bind to B Lymphocyte Stimulator comprise a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1 and/or any one of the VL domains referred to in Table 1. In preferred embodiments, scFvs of the present invention comprise the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention comprise the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs referred to in Table 1 and/or any one, two, three, or more of the VL CDRs referred to in Table 1. In preferred embodiments, scFvs of the present invention comprise the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention comprise the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, antibody fragments or variants of the scFvs referred to in Table 1 that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

(Table 1 can be found at the end of the specification just prior to the claims.)

In another embodiment of the present invention, an scFv that immunospecifically binds to a soluble form of B Lymphocyte Stimulator, comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1563-1880 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to a soluble form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1570-1595. In an even more preferred embodiment, an scFv that immunospecifically binds to a soluble form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1563-1569.

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In another embodiment of the present invention, an scFv that immunospecifically binds to a membrane-bound form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1881-2128 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to a membrane-bound form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1886-1908. In an even more preferred embodiment, an scFv that immunospecifically binds to a membrane-bound form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1881-1885.

In another embodiment of the present invention, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1-1562 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:834-872. In another preferred embodiment, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of B Lymphocyte Stimulator comprises, or alternatively consists of, any one of the amino acid sequences of SEQ ID NOS:1-46 or 321-329. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to the soluble form of B Lymphocyte Stimulator and/or the membrane-bound form of B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

In another embodiment of the present invention, scFvs that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1563-1880 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS:1563-1880 as disclosed in Table 1. In preferred 40 embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to 50 the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs SEQ ID NOS: 1563-1880 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in contained SEQ ID NOS:1563-1880, as disclosed in Table 1. In preferred 55 embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in 60 Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the soluble form of B Lymphocyte Stimu-

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tor, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS:1563-1880 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to B Lymphocyte Stimulator, preferably the soluble form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

In another embodiment of the present invention, scFvs that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1881-2128 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH CDRs contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1 and/or any one of the VL CDRs contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the

amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to B Lymphocyte Stimulator, preferably the membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

In another embodiment of the present invention, scFvs that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1-1562 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS:1-1562 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS:1-1562 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in SEQ ID NOS:1-1562 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH CDRs contained in SEQ ID NOS:1-1562 as disclosed in Table 1 and/or any one of the VL CDRs contained in SEQ ID NOS:1-1562, as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs or molecules, that immunospecifically bind to B Lymphocyte Stimulator, preferably the soluble and membrane-bound forms of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody

fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of B Lymphocyte Stimulator. In particular, the invention provides antibodies corresponding to the scFvs referred to in Table 1, such scFvs may routinely be "converted" to immunoglobulin molecules by inserting, for example, the nucleotide sequences encoding the VH and/or VL domains of the scFv into an expression vector containing the constant domain sequences and engineered to direct the expression of the immunoglobulin molecule, as described in more detail in Example 20, infra.

In one embodiment, the invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one of the VH domains contained in the sequences referred to in Table 1. The present invention also provides antibodies that immunospecifically bind to a polypeptide, or polypeptide fragment of B Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one, two, three, or more of the VH CDRs contained in the sequences referred to in Table 1. Molecules comprising, or alternatively consisting of, these antibodies, or antibody fragments or variants thereof, that immunospecifically bind to B Lymphocyte Stimulator or a B Lymphocyte Stimulator fragment are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments and/or variants.

In one embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind B Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR referred to in Table 1. In particular, the invention provides antibodies that immunospecifically bind B Lymphocyte Stimulator, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a VH CDR1 contained in SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885 as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind B Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR2 contained in SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885 as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind B Lymphocyte Stimulator, comprise, or alternatively consist of a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885 as disclosed in Table 1. In yet another embodiment, antibodies that immunospecifically bind B Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR1 contained in SEQ ID NOS:834-872, 1570-1595, or 1886-1908 as disclosed in Table 1; a VH CDR2 contained in SEQ ID NOS: SEQ ID NOS: SEQ ID NOS:834-872, 1570-1595, or 1886-1908; and/or a VH CDR3 contained in SEQ ID NOS: SEQ ID NOS:834-872, 1570-1595, or 1886-1908 as disclosed in Table 1. Preferably, antibodies of the invention comprise, or alternatively consist of, VH CDRs that are derived from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) that immunospecifically bind to a polypeptide, or polypeptide fragment of B Lymphocyte Stimulator. In particular, the invention provides antibodies wherein said antibodies comprise, or alternatively consist of, a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. The present invention also provides antibodies that immunospecifically bind to a polypeptide or polypeptide fragment of B Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a VL CDR having an amino acid sequence of any one, two, three, or more of the VL CDRs contained in the sequences referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

In one embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind B Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR referred to in Table 1. In particular, the invention provides antibodies that immunospecifically bind B Lymphocyte Stimulator, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a VL CDR1 contained in SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885 as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind B Lymphocyte Stimulator comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR2 contained in SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885 as disclosed in Table 1. In a preferred embodiment, antibodies comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885 disclosed in Table 1. In yet another embodiment, antibodies that immunospecifically bind B Lymphocyte Stimulator comprise, or alternatively consist of: a polypeptide having the amino acid sequence of a VL CDR1 contained in SEQ ID NOS: 834-872, 1570-1595, or 1886-1908 as disclosed in Table 1; a VL CDR2 SEQ ID NOS:834-872, 1570-1595, or 1886-1908 as disclosed in Table 1; and a VL CDR3 contained in SEQ ID NOS:834-872, 1570-1595, or 1886-1908 as disclosed in Table 1. Preferably, antibodies of the invention comprise, or alternatively consist of, VL CDRs that are derived from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of B Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a VH domain of one of the scFvs referred to in Table 1 combined with a VL domain of one of the scFvs referred to in Table 1, or other VL domain. The present invention further provides antibodies (including molecules comprising, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of B Lymphocyte

Stimulator, wherein said antibodies comprise, or alternatively consist of, a VL domain of one of the scFvs referred to in Table 1 combined with a VH domain of one of the scFvs referred to in Table 1, or other VH domain. In a preferred embodiment, antibodies that immunospecifically bind to a polypeptide or a polypeptide fragment of B Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1 and a VL domain contained in contained SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1. In a further preferred embodiment, the antibodies of the invention comprise, or alternatively consist of, a VH and a VL domain from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) that immunospecifically bind to a polypeptide or polypeptide fragment of B Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, one, two, three, or more VH CDRs and one, two, three or more VL CDRs, as referred to in Table 1. In particular, the invention provides for antibodies that immunospecifically bind to a polypeptide or polypeptide fragment of B Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a VH CDR1 and a VL CDR1, a VH CDR1 and a VL CDR2, a VH CDR1 and a VL CDR3, a VH CDR2 and a VL CDR1, VH CDR2 and a VL CDR2, a VH CDR2 and a VL CDR3, a VH CDR3 and a VL CDR1, a VH CDR3 and a VL CDR2, a VH CDR3 and a VL CDR3, or any combination thereof, of the VH CDRs and VL CDRs referred to in Table 1. In a preferred embodiment, one or more of these combinations are from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

In a preferred embodiment the invention provides antibodies wherein the VH CDRX (where X=1, 2, or 3) and VL CDRY (where Y=1, 2, or 3) are from scFvs with the same specificity (i.e., from scFvs that bind soluble B Lymphocyte Stimulator, from scFvs that bind membrane-bound B Lymphocyte Stimulator, or from scFvs that bind both soluble and membrane-bound B Lymphocyte Stimulator. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. As such, the term "antibody" encompasses not only whole antibody molecules, but also antibody fragments, as well as variants (including derivatives) of antibodies and antibody fragments. Antibodies of the invention include, but are not limited to, monoclonal, multispecific, human or chimeric antibodies, single chain antibodies, single chain Fvs (scFvs), Fab fragments, F(ab')<sub>2</sub> fragments, Fd frag-

ments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub>, IgG<sub>4</sub>, IgA, and IgA<sub>2</sub>) or subclass of immunoglobulin molecule. The antibodies of the present invention also include molecules comprising, or alternatively consisting of, a polypeptide having an amino acid sequence of a portion of an amino acid sequence contained SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908. Preferably, an antibody of the invention comprises, or alternatively consists of, a polypeptide having an amino acid sequence of a VH domain, VH CDR, VL domain, or VL CDR of any one those contained in the sequences referred to in Table 1. Antibodies of the invention also include molecules comprising, or alternatively consisting of, fragments or variants of the above antibodies that immunospecifically bind B Lymphocyte Stimulator.

Most preferably the antibodies of the present invention are whole antibodies or antibody fragments that immunospecifically bind human B Lymphocyte Stimulator. Antibody fragments of the invention that immunospecifically bind human B Lymphocyte Stimulator include, but are not limited to, Fab, Fab' and Fab', Fd fragments, single-chain Fvs (scFvs), single-chain antibodies, disulfide-linked Fvs (sdFvs), fragments comprising, or alternatively consisting of, either a VL or VH domain, and epitope binding fragments of any of the above.

B Lymphocyte Stimulator-binding antibody fragments, including single-chain antibodies, may comprise, or alternatively consist of, the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. In a preferred embodiment, the antibodies of the invention comprise, or alternatively consist of, a polypeptide that immunospecifically binds to B Lymphocyte Stimulator, said polypeptides comprise, or alternatively consist of, one, two, three, four, five, six or more CDRs referred to in Table 1, preferably a polypeptide having an amino acid sequence of a VH CDR3 and/or a VL CDR3 of contained SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1. Most preferably, antibodies of the invention comprise, or alternatively consist of, one, two, three, four, five, six or more CDRs from the same scFv, as referred to in Table 1. The antibodies of the invention may be from any animal origin, including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken. Most preferably, the antibodies are human antibodies. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries and xenomeric or other organisms that have been genetically engineered to produce human antibodies. For a detailed discussion of a few of the technologies for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Pat. Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598; and Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995), which are incorporated by reference herein in their entirety. Human antibodies or "humanized" chimeric monoclonal antibodies can be produced using

techniques described herein or otherwise known in the art. For example, methods for producing chimeric antibodies are known in the art. See, for review the following references which are hereby incorporated in their entirety: Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Cabilly et al., U.S. Pat. No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boullianne et al., *Nature* 312:643 (1984); Neuberger et al., *Nature* 314:268 (1985). In addition, companies such as Abgenix, Inc. (Freemont, Calif.) and Genpharm (San Jose, Calif.) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

The antibodies of the present invention may be monovalent, bivalent, trivalent or multivalent. For example, monovalent scFvs can be multimerized either chemically or by association with another protein or substance. An scFv that is fused to a hexahistidine tag or a Flag tag can be multimerized using Ni-NTA agarose (Qiagen) or using anti-Flag antibodies (Stratagene, Inc.).

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a B Lymphocyte Stimulator polypeptide, or fragment thereof, or may be specific for both a B Lymphocyte Stimulator polypeptide, or fragment thereof, and a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08360; WO 91/00360; WO 92/05793; Tutt, et al., *J. Immunol.* 147:60-69 (1991); U.S. Pat. Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., *J. Immunol.* 148:1547-1553 (1992).

The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may bind immunospecifically to murine B Lymphocyte Stimulator (e.g., a polypeptide having the amino acid sequence of human B Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or B Lymphocyte Stimulator expressed on human monocytes; murine B Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or B Lymphocyte Stimulator expressed on murine monocytes; rat B Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey B Lymphocyte Stimulator (e.g., the monkey B Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey B Lymphocyte Stimulator, or B Lymphocyte Stimulator expressed on monkey monocytes), preferably the antibodies of the invention bind immunospecifically to human B Lymphocyte Stimulator. Preferably, the antibodies of the invention bind immunospecifically to human and monkey B Lymphocyte Stimulator. Also preferably, the antibodies of the invention bind immunospecifically to human B Lymphocyte Stimulator and murine B Lymphocyte Stimulator. More preferably, antibodies of the invention, bind immunospecifically and with higher affinity to human B Lymphocyte Stimulator than to murine B Lymphocyte Stimulator.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described



herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, antibodies of the present invention cross-react with APRIL (SEQ ID NO:3239; GenBank Accession No. AF046888; J. Exp. Med. 188(6):1185-1190; PCT International Publication WO97/33902). In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under hybridization conditions (as described herein).

In preferred embodiments, the antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), immunospecifically bind to B Lymphocyte Stimulator and do not cross-react with any other antigens. In more preferred embodiments, the antibodies of the present invention immunospecifically bind to B Lymphocyte Stimulator and do not cross-react with TRAIL, APRIL, Endokine-alpha, TNF-alpha, TNF-beta, Fas-L or LIGHT.

The present invention also provides for a nucleic acid molecule, generally

isolated, encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). In one embodiment, a nucleic acid molecule of the invention encodes an antibody comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR1 having an amino acid sequence of any one of the VH CDR1s referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR2 having an amino acid sequence of any one of the VH CDR2s referred to in Table 1. In yet another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR3 having an amino acid sequence of any one of the VH CDR3s referred to in Table 1. Nucleic acid molecules encoding antibodies that immunospecifically bind B Lymphocyte Stimulator and comprise, or alternatively consist of, fragments or variants of the VH domains and/or VH CDRs are also encompassed by the invention.

In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR1 having an amino acid sequence of any one of the VL CDR1s referred to in Table 1. In another embodi-

ment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR2 having an amino acid sequence of any one of the VL CDR2s referred to in Table 1. In yet another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR3 having an amino acid sequence of any one of the VL CDR3s referred to in Table 1. Nucleic acid encoding antibodies that immunospecifically bind B Lymphocyte Stimulator and comprise, or alternatively consist of, fragments or variants of the VL domains and/or VL CDR(s) are also encompassed by the invention.

In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains referred to in Table 1 and a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the invention encodes an antibody comprising, or alternatively consisting of, a VH CDR1, a VL CDR1, a VH CDR2, a VL CDR2, a VH CDR3, a VL CDR3, or any combination thereof having an amino acid sequence referred to in Table 1. Nucleic acid encoding antibodies that immunospecifically bind B Lymphocyte Stimulator and comprise, or alternatively consist of, fragments or variants of the VL and/or domains and/or VH CDR(s) and/or VL CDR(s) are also encompassed by the invention.

The present invention also provides antibodies that comprise, or alternatively consist of, variants (including derivatives) of the VH domains, VH CDRs, VL domains, and VL CDRs described herein, which antibodies immunospecifically bind to B Lymphocyte Stimulator. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which result in amino acid substitutions. Preferably, the variants (including derivatives) encode less than 50 amino acid substitutions, less than 40 amino acid substitutions, less than 30 amino acid substitutions, less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the reference VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, or VL CDR3. In specific embodiments, the variants encode substitutions of VH CDR3. In a preferred embodiment, the variants have conservative amino acid substitutions at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence,

such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity (e.g., the ability to bind B Lymphocyte Stimulator). Following mutagenesis, the encoded protein may routinely be expressed and the functional and/or biological activity of the encoded protein, (e.g., ability to immunospecifically bind B Lymphocyte Stimulator) can be determined using techniques described herein or by routinely modifying techniques known in the art.

The antibodies of the invention include derivatives (i.e., variants) that are modified, e.g., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not affect the ability of the antibody to immunospecifically bind to B Lymphocyte Stimulator. For example, but not by way of limitation, derivatives of the invention include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

In a specific embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds B Lymphocyte Stimulator, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH or VL domains referred to in Table 1 under stringent conditions, e.g., hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45° C. followed by one or more washes in 0.2xSSC/0.1% SDS at about 50–65° C., under highly stringent conditions, e.g., hybridization to filter-bound nucleic acid in 6xSSC at about 45° C. followed by one or more washes in 0.1xSSC/0.2% SDS at about 68° C., or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F. M. et al., eds., 1989, *Current Protocols in Molecular Biology*, Vol. 1, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1–6.3.6 and 2.10.3). In another embodiment, an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH CDRs or VL CDRs referred to in Table 1 under stringent conditions, e.g., hybridization under conditions as described above, or under other stringent hybridization conditions which are known to those of skill in the art. In another embodiment, an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH CDRs referred to in Table 1 under stringent conditions e.g., hybridization under conditions as described above, or under other stringent hybridization conditions which are known to those of skill in the art. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

In another embodiment, an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds

to B Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VH domains referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VH CDRs referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any one of the VH CDRs referred to in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

In another embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to B Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL domains referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL CDRs referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL CDRs referred to in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may also be described or specified in terms of their binding affinity for B Lymphocyte Stimulator polypeptides or fragments or variants of B Lymphocyte Stimulator polypeptides (e.g., to the soluble form of B Lymphocyte Stimulator and/or membrane-bound form of B Lymphocyte Stimulator). In specific embodiments, antibodies of the invention bind B Lymphocyte Stimulator polypeptides, or fragments or variants thereof, with a dissociation constant or  $K_D$  of less than or equal to  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M, or  $10^{-5}$  M. More preferably, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,

or  $10^{-8}$  M. Even more preferably, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M. The invention encompasses antibodies that bind B Lymphocyte Stimulator polypeptides with a dissociation constant or  $K_D$  that is within any one of the ranges that are between each of the individual recited values.

In specific embodiments, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with an off rate ( $k_{off}$ ) of less than or equal to  $5 \times 10^{-2}$  sec $^{-1}$ ,  $10^{-2}$  sec $^{-1}$ ,  $5 \times 10^{-3}$  sec $^{-1}$  or  $10^{-3}$  sec $^{-1}$ . More preferably, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with an off rate ( $k_{off}$ ) less than or equal to  $5 \times 10^{-4}$  sec $^{-1}$ ,  $10^{-4}$  sec $^{-1}$ ,  $5 \times 10^{-5}$  sec $^{-1}$ , or  $10^{-5}$  sec $^{-1}$ . The invention encompasses antibodies that bind B Lymphocyte Stimulator polypeptides with an off rate ( $k_{off}$ ) that is within any one of the ranges that are between each of the individual recited values.

In other embodiments, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with an on rate ( $k_{on}$ ) of greater than or equal to  $10^3$  M $^{-1}$  sec $^{-1}$ ,  $5 \times 10^3$  M $^{-1}$  sec $^{-1}$ ,  $10^4$  M $^{-1}$  sec $^{-1}$  or  $5 \times 10^4$  M $^{-1}$  sec $^{-1}$ . More preferably, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with an on rate ( $k_{on}$ ) greater than or equal to  $10^5$  M $^{-1}$  sec $^{-1}$ ,  $5 \times 10^5$  M $^{-1}$  sec $^{-1}$ ,  $10^6$  M $^{-1}$  sec $^{-1}$ , or  $5 \times 10^6$  M $^{-1}$  sec $^{-1}$  or  $10^7$  M $^{-1}$  sec $^{-1}$ . The invention encompasses antibodies that bind B Lymphocyte Stimulator polypeptides with an on rate ( $k_{on}$ ) that is within any one of the ranges that are between each of the individual recited values.

The invention also encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that have one or more of the same biological characteristics as one or more of the antibodies described herein. By "biological characteristics" is meant, the in vitro or in vivo activities or properties of the antibodies, such as, for example, the ability to bind to B Lymphocyte Stimulator (e.g., the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, the soluble form and membrane-bound form of B Lymphocyte Stimulator), and/or an antigenic and/or epitope region of B Lymphocyte Stimulator), the ability to substantially block B Lymphocyte Stimulator/B Lymphocyte Stimulator receptor (e.g., TAC1—GenBank accession number AAC51790 and/or BCMA—GenBank accession number NP\_001183) binding, or the ability to block B Lymphocyte Stimulator mediated biological activity (e.g., stimulation of B cell proliferation and immunoglobulin production). Optionally, the antibodies of the invention will bind to the same epitope as at least one of the antibodies specifically referred to herein. Such epitope binding can be routinely determined using assays known in the art.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that neutralize B Lymphocyte Stimulator or a fragment thereof, said antibodies comprising, or alternatively consisting of, a portion (i.e., a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv referred to in Table 1, more preferably having an amino acid sequence contained in SEQ ID NOS:834-872, 1570-1595, or 1886-1908, and even more preferably having an amino acid sequence contained in SEQ ID NOS:1-46, 321-329,

1563-1569, or 1881-1885 as disclosed in Table 1, or a fragment or variant thereof. By an antibody that "neutralizes B Lymphocyte Stimulator or a fragment thereof" is meant an antibody that diminishes or abolishes the ability of B Lymphocyte Stimulator to bind to its receptor (e.g., TAC1 and BCMA) to stimulate B cell proliferation, to stimulate immunoglobulin secretion by B cells, and/or to stimulate the B Lymphocyte Stimulator receptor signalling cascade. In one embodiment, an antibody that neutralizes B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR domain in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that neutralizes B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that neutralizes B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that neutralizes B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that inhibit (i.e., diminish or abolish) B Lymphocyte Stimulator mediated B cell proliferation as determined by any method known in the art such as, for example, the assays described in Examples 21 and 22, infra, said antibodies comprising, or alternatively consisting of, a portion (e.g., a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS:834-872, 1570-1595, 1886-1908, and even more preferably having an amino acid sequence SEQ ID NOS:1-46, 321-329, 1563-1569, 1881-1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that inhibits B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908, as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that inhibits B Lymphocyte Stimulator mediated B

cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that inhibits B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that inhibits B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that enhance the activity of B Lymphocyte Stimulator or a fragment thereof, said antibodies comprising, or alternatively consisting of, a portion (i.e., a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS: 834-872, 1570-1595, or 1886-1908, and preferably having an amino acid sequence of SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885, as disclosed in Table 1, or a fragment or variant thereof. By an antibody that "enhances the activity of B Lymphocyte Stimulator or a fragment thereof" is meant an antibody increases the ability of B Lymphocyte Stimulator to bind to its receptor (e.g., TAC1 or BCMA), to stimulate B cell proliferation, to stimulate immunoglobulin secretion by B cells, and/or to stimulate the B Lymphocyte Stimulator receptor signalling cascade. In one embodiment, an antibody that enhances the activity of B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances the activity of B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances the activity of B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that enhances the activity of B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1,

or a fragment or variant thereof. In another preferred embodiment, an antibody that enhances the activity of B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that stimulate B Lymphocyte Stimulator mediated B cell proliferation as determined by any method known in the art, such as, for example, the assays described in Examples 21 and 22, *infra*, said antibodies comprising, or alternatively consisting of, a portion (e.g., a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence of SEQ ID NOS: 834-872, 1570-1595, or 1886-1908, and even more preferably having an amino acid sequence of SEQ ID NOS: 1-46, 321-329, 1563-1569, or 1881-1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that stimulates B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that stimulates B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that stimulates B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that stimulates B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for fusion proteins comprising, or alternatively consisting of, an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that immunospecifically binds to B Lymphocyte Stimulator, and a heterologous polypeptide. Preferably, the heterologous polypeptide to which the antibody is fused is useful for B-cell function or is useful to target the antibody to B-cells. In an alternative preferred embodiment, the heterologous polypeptide to which the antibody is fused is useful for monocyte cell function or is useful to target the antibody to a monocyte. In another embodiment, the heterologous polypeptide to which the antibody is fused is albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Pat. No. 5,876,969, issued Mar. 2, 1999, EP Patent 0 413 622, and U.S. Pat. No. 5,766,883, issued Jun. 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, antibodies of the

present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1-585 of human serum albumin as shown in FIGS. 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-x of human serum albumin, where x is an integer from 1 to 585 and the albumin fragment has human serum albumin activity. In another preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Pat. No. 5,766,883 herein incorporated by reference in its entirety. Antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide).

In one embodiment, a fusion protein of the invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one or more of the VH domains referred to in Table 1 or the amino acid sequence of any one or more of the VL domains referred to in Table 1 or fragments or variants thereof, and a heterologous polypeptide sequence. In another embodiment, a fusion protein of the present invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs referred to in Table 1, or the amino acid sequence of any one, two, three, or more of the VL CDRs referred to in Table 1, or fragments or variants thereof, and a heterologous polypeptide sequence. In a preferred embodiment, the fusion protein comprises, or alternatively consists of, a polypeptide having the amino acid sequence of, a VH CDR3 referred to in Table 1, or fragment or variant thereof, and a heterologous polypeptide sequence, which fusion protein immunospecifically binds to B Lymphocyte Stimulator. In another embodiment, a fusion protein comprises, or alternatively consists of a polypeptide having the amino acid sequence of at least one VH domain referred to in Table 1 and the amino acid sequence of at least one VL domain referred to in Table 1 or fragments or variants thereof, and a heterologous polypeptide sequence. Preferably, the VH and VL domains of the fusion protein correspond to the same scFv referred to in Table 1. In yet another embodiment, a fusion protein of the invention comprises, or alternatively consists of a polypeptide having the amino acid sequence of any one, two, three or more of the VH CDRs referred to in Table 1 and the amino acid sequence of any one, two, three or more of the VL CDRs referred to in Table 1, or fragments or variants thereof, and a heterologous polypeptide sequence. Preferably, two, three, four, five, six, or more of the VHCDR(s) or VLCDR(s) correspond to the same scFv referred to in Table 1. Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention.

The present invention also provides: antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that immunospecifically bind to the soluble form of B Lymphocyte Stimulator; antibodies that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator; and antibodies that immunospecifically bind to both the soluble form and membrane-bound form of B Lymphocyte Stimulator.

In one embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1, or fragment(s) or variant(s) (including derivative) thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the soluble form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the soluble form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

In another embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1, or a fragment or variant thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in

SEQ ID NOS: 1881–2128 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

In another embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator, are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1–1562 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1–1562 as disclosed in Table 1, or a fragment or variant thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1–1562 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1–1562 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1–1562, disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS: 1–1562, disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1.

The present invention also provides for mixtures of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator, wherein the mixture has at least one, two, three, four, five or more different antibodies of the invention. In particular, the invention provides for mixtures of different antibodies that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the membrane-bound form and soluble form of B Lymphocyte Stimulator. In specific embodiments, the invention provides mixtures of at least 2, preferably at least 4, at least 6, at least 8, at least 10, at least 12, at least 15, at least 20, or at least 25 different antibodies that immunospecifically bind to B Lymphocyte Stimulator, wherein at least 1, at least 2, at least 4, at least 6, or at least 10, antibodies of the mixture is an antibody of the invention. In a specific embodiment, each antibody of the mixture is an antibody of the invention.

The present invention also provides for panels of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator, wherein the panel has at least one, two, three, four, five or more different antibodies of the invention. In particular, the invention provides for panels of different antibodies that immunospecifically bind to the soluble form

of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the membrane-bound form and soluble form of B Lymphocyte Stimulator. In specific embodiments, the invention provides for panels of antibodies that have different affinities for B Lymphocyte Stimulator, different specificities for B Lymphocyte Stimulator, or different dissociation rates. The invention provides panels of at least 10, preferably at least 25, at least 50, at least 75, at least 100, at least 125, at least 150, at least 175, at least 200, at least 250, at least 300, at least 350, at least 400, at least 450, at least 500, at least 550, at least 600, at least 650, at least 700, at least 750, at least 800, at least 850, at least 900, at least 950, or at least 1000, antibodies. Panels of antibodies can be used, for example, in 96 well plates for assays such as ELISAs.

The present invention further provides for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1563–1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDRs contained in SEQ ID NOS: 1563–1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS: 1563–1880 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1563–1880, as disclosed in Table 1 or a variant thereof.

The present invention further provides for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1881–2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDRs contained in SEQ ID NOS: 1881–2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS: 1881–2128 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid

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sequence of any one or more of the VH CDR3s contained in SEQ ID NOS:1881-2128 as disclosed in Table 1 or a variant thereof.

The present invention further provides for compositions comprising, one or more antibodies (including scFvs, or molecules comprising, or alternatively consisting of antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s contained in SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS:1-1562 as disclosed in Table 1 or a variant thereof.

Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS:1563-1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s contained in SEQ ID NOS:1563-1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s contained in SEQ ID NOS:1563-1880 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1563-1880 as disclosed in Table 1, or a variant thereof.

Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively

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consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS:1881-2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s contained in SEQ ID NOS:1881-2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s SEQ ID NOS:1881-2128 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1881-2128 as disclosed in Table 1, or a variant thereof.

Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s contained in SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof.

In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains in disclosed in Table 1, or a variant thereof, and an amino acid sequence of any one or more of the VL domains disclosed in Table 1, or a variant thereof wherein the VH and VL domains are from scFvs with the same specificity (i.e., from scFvs that bind soluble B Lymphocyte Stimulator (SEQ ID NOS:1563-1880), from scFvs that bind membrane-bound B Lymphocyte Stimulator (SEQ ID 1881-2128), or from scFvs that bind both soluble and membrane-bound B Lymphocyte Stimulator (SEQ ID NOS:1-1562). In a preferred embodiment the invention provides antibodies wherein the VH CDR3 (where X=1,2, or 3) and VL CDR3 (where Y=1,2, or 3) are from scFvs with the same specificity (i.e., from scFvs that bind soluble B Lymphocyte

Stimulator (SEQ ID NOS:1563-1880), from scFvs that bind membrane-bound B Lymphocyte Stimulator (SEQ ID NOS: 1881-2128), or from scFvs that bind both soluble and membrane-bound B Lymphocyte Stimulator (SEQ ID NOS: 1-1562). In yet another embodiment, a composition of the present invention comprises one or more fusion proteins.

As discussed in more detail below, a composition of the invention may be used either alone or in combination with other compositions. The antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the present invention) may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Pat. No. 5,314,995; and EP 396,387.

Antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the present invention) may be used, for example, but not limited to, to purify and detect B Lymphocyte Stimulator, and to target the polypeptides of the present invention to cells expressing membrane-bound B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of B Lymphocyte Stimulator in biological samples. See, e.g., Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

#### Methods Producing Antibodies

The antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

The single chain Fvs disclosed in Table 1 were generated using phage display methods known in the art. Furthermore, other scFvs that immunospecifically bind B Lymphocyte Stimulator may be generated using phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (e.g., human or murine cDNA libraries of lymphoid tissues) or synthetic cDNA libraries. The DNA encoding the VH and VL domains are joined together by an scFv linker by PCR and cloned into a phagemid vector (e.g., p CANTAB 6 or pComb 3 HSS). The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13 and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to an antigen of interest (i.e., B Lymphocyte Stimulator or a fragment thereof) can be selected or identified with antigen,

e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies of the present invention include, but are not limited to, those disclosed in Brinkman et al., *J. Immunol. Methods* 182:41-50 (1995); Ames et al., *J. Immunol. Methods* 184:177-186 (1995); Kettleborough et al., *Eur. J. Immunol.* 24:952-958 (1994); Persic et al., *Gene* 187 9-18 (1997); Burton et al., *Advances in Immunology* 57:191-280(1994); PCT publications WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; WO97/13844; and U.S. Pat. Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described below. Techniques to recombinantly produce Fab, Fab', and F(ab')<sub>2</sub> fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); Sawai et al., *AJRL* 34:26-34 (1995); and Better et al., *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

To generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a VH constant region, e.g., the human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, e.g., human kappa or lambda constant regions. Preferably, the vectors for expressing the VH or VL domains comprise a promoter suitable to direct expression of the heavy and light chains in the chosen expression system, a secretion signal, a cloning site for the immunoglobulin variable domain, immunoglobulin constant domains, and a selection marker such as neomycin. The VH and VL domains may also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, e.g., IgG, using techniques known to those of skill in the art.

Cell lines that express antibodies that comprise the VH and VL domains of scFvs of the invention have been deposited with the American Type Culture Collection ("ATCC") on the dates listed in Table 2 and given the ATCC Deposit Numbers identified in Table 2. The American Type Culture Collection is located at 10801 University Boulevard, Manassas, Va. 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.



Cell Line	Corresponding scFv	SEQ ID NO:	ATCC Deposit Number	ATCC Deposit Date
NSO-B11-15	1050B11-15	24	PTA-3238	Mar. 27, 2001
NSO-anti-BlyS-6D08-18	10606D08	2	PTA-3239	Mar. 27, 2001
NSO-anti-BlyS-116A01-60	1116A01	327	PTA-3240	Mar. 27, 2001
1026C04K	1026C04-K	1563	PTA-3241	Mar. 27, 2001
1050A12	1050A12	12	PTA-3242	Mar. 27, 2001
1050-B11	1050B11	9	PTA-3243	Mar. 27, 2001

Accordingly, in one embodiment, the invention provides antibodies that comprise the VH and VL domains of scFvs of the invention.

In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-B11-15.

In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-anti-BlyS-6D08-18.

In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-anti-BlyS-116A01-60.

In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line 1026C04K.

In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line 1050A12.

In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-B11.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide. In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by between 1% and 10% in a competitive inhibition assay. In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by between 1% and 10% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 10% and up to 20% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 20% and up to 30% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or

variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 30% and up to 40% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 40% and up to 50% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 50% and up to 60% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 60% and up to 70% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 70% and up to 80% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 80% and up to 90% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 90% and up to 100% in a competitive inhibition assay.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC™ deposit number PTA-3238 to a B Lymphocyte Stimulator polypeptide.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC™ deposit number PTA-3239 to a B Lymphocyte Stimulator polypeptide.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC™ deposit number PTA-3240 to a B Lymphocyte Stimulator polypeptide.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC™ deposit number PTA-3241 to a B Lymphocyte Stimulator polypeptide.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC™ deposit number PTA-3242 to a B Lymphocyte Stimulator polypeptide.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCC™ deposit number PTA-3243 to a B Lymphocyte Stimulator polypeptide.

For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use human or chimeric antibodies. Completely human antibodies are particularly desirable for therapeutic treatment of human patients. See also, U.S. Pat. Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO98/16654, WO 96/34096, WO 96/33735, and WO 91/10741, each of which is incorporated herein by reference in its entirety. In a specific embodiment, antibodies of the present invention comprise one or more VH and VL domains corresponding to the human scFvs of the invention and framework regions from another immunoglobulin molecule, preferably a human immunoglobulin molecule. In a specific embodiment, antibodies of the present invention comprise one or more CDRs corresponding to the human scFvs of the invention and framework regions from another immunoglobulin molecule, preferably a human immunoglobulin molecule. In other embodiments, an antibody of the present invention comprises one, two, three, four, five, six or more VL CDRs or VH CDRs corresponding to one or more of the human scFvs referred to in Table 1, or fragments or variants thereof, and framework regions (and, optionally CDRs not derived from the scFvs in Table 1) from a human immunoglobulin molecule. In a preferred embodiment, an antibody of the present invention comprises a VH CDR3, VL CDR3, or both, corresponding to the same scFv, or different scFvs referred to in Table 1, or fragments or variants thereof, and framework regions from a human immunoglobulin.

A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules such as antibodies having a variable region derived from a human antibody and a non-human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., J. Immunol. Methods 125:191-202 (1989); U.S. Pat. Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Chimeric antibodies comprising one or more CDRs from human species and framework regions from a non-human immunoglobulin molecule (e.g., framework regions from a canine or feline immunoglobulin molecule) can be produced using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Pat. Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Pat. No. 5,565,332). In a preferred embodiment,

chimeric antibodies comprise a human CDR3 having an amino acid sequence of any one of the VH CDR3s or VL CDR3s referred to in Table 1, or a variant thereof, and non-human framework regions or human framework regions different from those of the frameworks in the corresponding scFv disclosed in Table 1. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Pat. No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.)

Further, the antibodies of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" B Lymphocyte Stimulator polypeptides using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444 (1993); and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies of the invention which bind to B Lymphocyte Stimulator and competitively inhibit the binding of B Lymphocyte Stimulator to its receptor (as determined by assays well known in the art such as, for example, that disclosed, *infra*) can be used to generate anti-idiotypes that "mimic" a B Lymphocyte Stimulator ligand/receptor-binding domain and, as a consequence, bind to and neutralize B Lymphocyte Stimulator receptors (e.g., TACI, BCMA, and TR20). Such neutralizing anti-idiotypes (including molecules comprising, or alternatively consisting of, antibody fragments or variants, such as Fab fragments of such anti-idiotypes) can be used in therapeutic regimens to neutralize B Lymphocyte Stimulator. For example, such anti-idiotypic antibodies can be used to bind B Lymphocyte Stimulator ligands/receptors, and thereby block B Lymphocyte Stimulator mediated biological activity. Alternatively, anti-idiotypes that "mimic" a B Lymphocyte Stimulator binding domain may bind to B Lymphocyte Stimulator receptor(s) and induce B Lymphocyte Stimulator receptor mediated signalling (e.g., activation of nuclear factor of activated T cells (NF-AT), nuclear factor-kappa B (NF-kappa B), and/or AP-1). Such agonistic anti-idiotypes (including agonistic Fab fragments of these anti-idiotypes) can be used in therapeutic regimens to induce or enhance B Lymphocyte Stimulator receptor mediated signalling. For example, such anti-idiotypic antibodies can be used to bind B Lymphocyte Stimulator ligands/receptors, and thereby stimulate B Lymphocyte Stimulator mediated biological activity (e.g., B cell proliferation and/or immunoglobulin production).

Once an antibody molecule of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) has been chemically synthesized or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, or more generally, a protein molecule, such as, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention may be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

### Polynucleotides Encoding an Antibody

The invention provides polynucleotides comprising, or alternatively consisting of, a nucleotide sequence encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). The invention also encompasses polynucleotides that hybridize under high stringency, or alternatively, under intermediate or lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides complementary to nucleic acids having a polynucleotide sequence that encodes an antibody of the invention or a fragment or variant thereof.

The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. Since the amino acid sequences of the scFv antibodies and VH domains, VL domains and CDRs thereof, are known (as described in Table 1), nucleotide sequences encoding these antibodies can be determined using methods well known in the art, i.e., the nucleotide codons known to encode the particular amino acids are assembled in such a way to generate a nucleic acid that encodes the antibody, of the invention. Such a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., *BioTechniques* 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence of the antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, *Molecular Cloning, A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. and Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, which are both incorporated by reference herein in their entirety), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, one or more of the VH and VL domains referred to in Table 1, or fragments or variants thereof, is inserted within framework regions using recom-

binant DNA techniques known in the art. In a specific embodiment, one, two, three, four, five, six, or more of the CDRs referred to in Table 1, or fragments or variants thereof, is inserted within framework regions using recombinant DNA techniques known in the art. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., *J. Mol. Biol.* 278: 457-479 (1998) for a listing of human framework regions, the contents of which are hereby incorporated by reference in its entirety). Preferably, the polynucleotides generated by the combination of the framework regions and CDRs encode an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically binds to B Lymphocyte Stimulator. Preferably, as discussed supra, polynucleotides encoding variants of antibodies or antibody fragments having one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules, or antibody fragments or variants, lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and fall within the ordinary skill of the art.

### Recombinant Expression of an Antibody

Recombinant expression of an antibody of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof (e.g., a heavy or light chain of an antibody of the invention or a portion thereof or a single chain antibody of the invention)), requires construction of an expression vector(s) containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule (e.g., a whole antibody, a heavy or light chain of an antibody, or portion thereof (preferably, but not necessarily, containing the heavy or light chain variable domain)), of the invention has been obtained, the vector(s) for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention (e.g., a whole antibody, a heavy or light chain of an antibody, a heavy or light chain variable domain of an antibody, or a portion thereof, or a heavy or light chain CDR, a single chain Fv, or fragments or variants thereof), operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Pat. No. 5,122,464, the contents of each of which are hereby incorporated by reference in its entirety) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy chain, the entire light chain, or both the entire heavy and light chains.

The expression vector(s) is(are) transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing polynucleotide(s) encoding an antibody of the invention (e.g., whole antibody, a heavy or light chain thereof, or portion thereof, or a single chain antibody of the invention, or a fragment or variant thereof), operably linked to a heterologous promoter. In preferred embodiments, for the expression of entire antibody molecules, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention *in situ*. These include, but are not limited to, microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foelcking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther et al., *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, *Nucleic Acids Res.* 13:3101-3109 (1985); Van Heeke & Schuster, *J. Biol. Chem.* 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified

from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) may be used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. Antibody coding sequences may be cloned individually into non-essential regions (for example, the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example, the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts (e.g., see Logan & Shenk, *Proc. Natl. Acad. Sci. USA* 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see, e.g., Bittner et al., *Methods in Enzymol.* 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERO, BHK, Hela, COS, NSO, MDCK, 293, 3T3, W138, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched

media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler et al., *Cell* 11:223 (1977)), hypoxanthineguanine phosphoribosyltransferase (Szybalska & Szybalski, *Proc. Natl. Acad. Sci. USA* 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., *Cell* 22:8 17 (1980)) genes can be employed in tk-, hgppt- or apt-cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., *Natl. Acad. Sci. USA* 77:357 (1980)); o-Hare et al., *Proc. Natl. Acad. Sci. USA* 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, *Proc. Natl. Acad. Sci. USA* 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 (*Clinical Pharmacy* 12:488-505; Wu and Wu, *Biotherapy* 3:87-95 (1991)); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); TIB TECH 11(5):155-215 (May, 1993)); and hygromycin, which confers resistance to hygromycin (Santerre et al., *Gene* 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); Krieger, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds.), *Current Protocols in Human Genetics*, John Wiley & Sons, NY (1994); Colberre-Garapin et al., *J. Mol. Biol.* 150:1 (1981), which are incorporated by reference herein in their entirety.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, *The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning*, Vol. 3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the coding sequence of the antibody, production of the antibody will also increase (Crouse et al., *Mol. Cell. Biol.* 3:257 (1983)).

The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain is preferably placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, *Nature* 322:52 (1986); Kohler, *Proc. Natl. Acad.*

*Sci. USA* 77:2 197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by recombinant expression, it may be purified by any method known in the art for purification of an immunoglobulin molecule, or more generally, for purification of a protein, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention may be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

#### Antibody Characterization

Antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be characterized in a variety of ways. In particular, antibodies and related molecules of the invention may be assayed for the ability to immunospecifically bind to B Lymphocyte Stimulator or a fragment of B Lymphocyte Stimulator (e.g., to the soluble form or the membrane-bound form of B Lymphocyte Stimulator) using techniques described herein or routinely modifying techniques known in the art. B Lymphocyte Stimulator or B Lymphocyte Stimulator fragments that may be immunospecifically bound by the compositions of the invention include, but are not limited to, human B Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or B Lymphocyte Stimulator expressed on human monocytes; murine B Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or B Lymphocyte Stimulator expressed on murine monocytes; rat B Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey B Lymphocyte Stimulator (e.g., the monkey B Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey B Lymphocyte Stimulator, or B Lymphocyte Stimulator expressed on monkey monocytes) or fragments thereof. Preferably compositions of the invention bind human B Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or fragments thereof. Assays for the ability of the antibodies of the invention to immunospecifically bind B Lymphocyte Stimulator or a fragment of B Lymphocyte Stimulator may be performed in solution (e.g., Houghten, *Bio/Techniques* 13:412-421 (1992)), on beads (e.g., Lam, *Nature* 354:82-84 (1991)), on chips (e.g., Fodor, *Nature* 364:555-556 (1993)), on bacteria (e.g., U.S. Pat. No. 5,223,409), on spores (e.g., U.S. Pat. Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (e.g., Cull et al., *Proc. Natl. Acad. Sci. USA* 89:1865-1869 (1992)) or on phage (e.g., Scott and Smith, *Science* 249:386-390 (1990); Devlin, *Science* 249:404-406 (1990); Cwirla et al., *Proc. Natl. Acad. Sci. USA* 87:6378-6382 (1990); and Felici, *J. Mol. Biol.* 222:301-310 (1991)) (each of these references is incorporated herein in its entirety by reference). Antibodies that have been identified to immunospecifically bind to B Lymphocyte Stimulator or a fragment of B Lymphocyte Stimulator can then be assayed for their specificity and affinity for B Lymphocyte Stimulator or a fragment of B Lymphocyte Stimulator using or routinely modifying techniques described herein or otherwise known in the art.

The antibodies of the invention may be assayed for immunospecific binding to B Lymphocyte Stimulator and

cross-reactivity with other antigens by any method known in the art. In particular, the ability of an antibody to immunospecifically bind to the soluble form or membrane-bound form of B Lymphocyte Stimulator and the specificity of the antibody, fragment, or variant for B Lymphocyte Stimulator polypeptide from a particular species (e.g., murine, monkey or human, preferably human) may be determined using or routinely modifying techniques described herein or otherwise known in art.

Immunoassays which can be used to analyze immunospecific binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al., eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immuno-precipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1 to 4 hours) at 40 degrees C., adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 40 degrees C., washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al., eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%-20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g.,  $^{32}\text{P}$  or  $^{125}\text{I}$ ) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion

regarding western blot protocols see, e.g., Ausubel et al., eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96-well microtiter plate with the antigen, washing away antigen that did not bind the wells, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the wells and incubating for a period of time, washing away unbound antibodies or non-specifically bound antibodies, and detecting the presence of the antibodies specifically bound to the antigen coating the well. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, the detectable molecule could be the antigen conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase). One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al., eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity of an antibody (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof) to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of the present invention for B Lymphocyte Stimulator and the binding off-rates can be determined from the data by Scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, B Lymphocyte Stimulator is incubated with an antibody of the present invention conjugated to a labeled compound (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) in the presence of increasing amounts of an unlabeled second anti-B Lymphocyte Stimulator antibody.

In a preferred embodiment, BiAcore kinetic analysis is used to determine the binding on and off rates of antibodies (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof) to B Lymphocyte Stimulator, or fragments of B Lymphocyte Stimulator. BiAcore kinetic analysis comprises analyzing the binding and dissociation of B Lymphocyte Stimulator from chips with immobilized antibodies on their surface as described in detail in Examples 6, 12, 17 and 18, *infra*.

The antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) can also be assayed for their ability to inhibit, increase, or not significantly alter, the binding of B Lymphocyte Stimulator to a B Lymphocyte Stimulator receptor (e.g., TACI and BCMA) using techniques known to those of skill in the art. For example, cells expressing a receptor for B Lymphocyte Stimulator (e.g., IM9, REH, ARH-77cells, Namalwa, and RPMI-8226 B cell tumor lines as well as peripheral CD20+ B cells) can be contacted with B Lymphocyte Stimulator in the presence or absence of an antibody, and the ability of the antibody to

inhibit, increase, or not significantly alter, B Lymphocyte Stimulator binding to the cells can be measured. B Lymphocyte Stimulator binding to cells can be measured by, for example, flow cytometry or a scintillation assay. B Lymphocyte Stimulator or the antibody can be labeled with a detectable compound such as a radioactive label (e.g.,  $^{32}\text{P}$ ,  $^{35}\text{S}$ , and  $^{125}\text{I}$ ) or a fluorescent label (e.g., fluorescein isothiocyanate, rhodamine, phycoerythrin, phycoerythrin, allophycocyanin,  $\alpha$ -phthalaldehyde and fluorescamine) to enable detection of an interaction between B Lymphocyte Stimulator and a B Lymphocyte Stimulator receptor and/or B Lymphocyte Stimulator and an antibody of the invention. Alternatively, the ability of antibodies of the invention to inhibit, increase, or not significantly alter, B Lymphocyte Stimulator binding to a B Lymphocyte Stimulator receptor can be determined in cell-free assays. For example, native or recombinant B Lymphocyte Stimulator (e.g., that having the amino acid sequence of amino acids 134-285 of SEQ ID NO:3228) or a fragment thereof can be contacted with an antibody and the ability of the antibody to inhibit, increase, or not significantly alter, B Lymphocyte Stimulator from binding to a B Lymphocyte Stimulator receptor can be determined. Preferably, the antibody is immobilized on a solid support and B Lymphocyte Stimulator or a B Lymphocyte Stimulator fragment is labeled with a detectable compound. Alternatively, B Lymphocyte Stimulator or a B Lymphocyte Stimulator fragment is immobilized on a solid support and the antibody is labeled with a detectable compound. B Lymphocyte Stimulator may be partially or completely purified (e.g., partially or completely free of other polypeptides) or part of a cell lysate. Further, the B Lymphocyte Stimulator polypeptide may be a fusion protein comprising B Lymphocyte Stimulator or a biologically active portion thereof and a domain such as an Immunoglobulin Fc or glutathione-S-transferase. For example, amino acid residues 1-154 of TACI (GenBank accession number AAC51790), or 1-48 of BCMA (GenBank accession number NP\_001183) may be fused to the Fc region of an IgG molecule and used in a cell free assay to determine the ability of antibodies of the invention to inhibit, increase, or not significantly alter, B Lymphocyte Stimulator binding to a B Lymphocyte Stimulator receptor. Alternatively, B Lymphocyte Stimulator can be biotinylated using techniques well known to those of skill in the art (e.g., biotinylation kit, Pierce Chemicals; Rockford, Ill.).

The antibodies of the invention (including scFvs or other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), can also be assayed for their ability to inhibit, stimulate, or not significantly alter, B Lymphocyte Stimulator-induced B-cell proliferation using techniques known to those of skill in the art. For example, B-cell proliferation can be assayed by  $^3\text{H}$ -thymidine incorporation assays and trypan blue cell counts (see, e.g., Moore et al., Science 285: 260-263 (1999)). Further, the antibodies of the invention, or fragments or variants thereof, can be assayed for their ability to block, stimulate, or not significantly alter, B Lymphocyte Stimulator-induced activation of cellular signaling molecules and transcription factors such as calcium-modulator and cyclophilin ligand ("CAML"), calcineurin, nuclear factor of activated T cells transcription factor ("NF-AT"), nuclear factor-kappa B ("NF-kappa B"), and AP-1 using techniques known to those of skill in the art (see, e.g., von Bulow and Bram, Science 278:138-141 (1997)). For example, NF-AT activity can be determined by electrophoretic gel shift assays, by detecting the expression of a protein known to be regulated by NF-AT (e.g., IL-2 expression), by detecting the induction of a reporter gene

(e.g., an NF-AT regulatory element operably linked to a nucleic acid encoding a detectable marker such as luciferase, beta-galactosidase or chloramphenicol acetyltransferase (CAT)), or by detecting a cellular response (e.g., cellular differentiation, or cell proliferation).

The antibodies of the invention, or fragments or variants thereof can also be assayed for their ability to neutralize, enhance, or not significantly alter, B Lymphocyte Stimulator activity. For example, antibodies or fragments or variants thereof, may be routinely tested for their ability to inhibit B Lymphocyte Stimulator from binding to cells expressing the receptor for B Lymphocyte Stimulator (see Example 3, *infra*).

#### 15 Selection and Screening for Antibodies that Immunospecifically Bind to Soluble B Lymphocyte Stimulator

Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be screened in a variety of assays to identify those antibodies that immunospecifically bind to the soluble form of B Lymphocyte Stimulator. In one particular assay, antibodies that bind to the biotinylated soluble form of B Lymphocyte Stimulator in solution are captured on streptavidin coated magnetic beads. This assay may be relatively applied to identify antibodies of the invention that neutralize and/or bind to B Lymphocyte Stimulator. Additionally, antibodies may be assayed in neutralization assays described herein or otherwise known in the art (see Example 3, *infra*). For example, antibodies may be tested for their ability to inhibit soluble B Lymphocyte Stimulator (e.g., biotinylated B Lymphocyte Stimulator) from binding to IM9 cells. In this assay, labeled soluble B Lymphocyte Stimulator (e.g., biotinylated B Lymphocyte Stimulator) is incubated with candidate anti-B Lymphocyte Stimulator antibodies to allow for the formation of B Lymphocyte Stimulator-anti-B Lymphocyte Stimulator antibody complexes. Following incubation, an aliquot of the B Lymphocyte Stimulator-anti-B Lymphocyte Stimulator antibody sample is added to IM9 cells. The binding of soluble B Lymphocyte Stimulator may be determined using techniques known in the art. For example, the binding of biotinylated B Lymphocyte Stimulator to IM9 cells may be detected using a fluorimeter following the addition of streptavidin-delfia. Biotinylated B Lymphocyte Stimulator, if it is not bound by antibodies that neutralize B Lymphocyte Stimulator, binds to the cells is detected. Thus, an antibody that decreases the amount of bio-B Lymphocyte Stimulator that binds to IM-9 cells (relative to a control sample in which the B Lymphocyte Stimulator had been preincubated with an irrelevant antibody or no antibody at all) is identified as one that binds to and neutralizes the soluble form of B Lymphocyte Stimulator. In another assay, antibodies are screened using ELISAs for those antibodies that bind to biotinylated soluble B Lymphocyte Stimulator, but do not bind membrane-bound B Lymphocyte Stimulator, such as, for example, B Lymphocyte Stimulator on membranes from U937 cells (see Examples 2 and 9, *infra*). In these assays, soluble B Lymphocyte Stimulator (e.g., biotinylated B Lymphocyte Stimulator) and membrane-bound B Lymphocyte Stimulator (e.g., on U937 membranes) are incubated in separate samples with the same antibodies and those antibodies that bind to the soluble B Lymphocyte Stimulator (biotinylated B Lymphocyte Stimulator), but not membrane-bound B Lymphocyte Stimulator (e.g., on U937 membranes) are captured and identified.

Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, anti-

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body fragments or variants thereof) may be tested to identify those antibodies that do not cross-react with APRIL, endokine-alpha, VEG1, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS (see Example 4, *infra*). Antibodies may also be tested for their affinity for B Lymphocyte Stimulator using, for example, BIAcore analysis (see Examples 6, 12, 17 and 18 *infra*). Antibodies may also be tested for their ability to stimulate, inhibit, or not alter, B Lymphocyte Stimulator-induced immunoglobulin production and/or B-cell proliferation using techniques known to those of skill in the art. For example, human B-cells, B Lymphocyte Stimulator and antibodies may be incubated together in 96 well plates and  $^3\text{H}$ -thymidine incorporation may be measured using a scintillation counter.

#### Selection and Screening for Antibodies that Immunospecifically Bind to Membrane-Bound B Lymphocyte Stimulator

Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be screened in a variety of assays to identify those antibodies that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator. In one particular assay, antibodies that bind to B Lymphocyte Stimulator on U937 membranes or immobilized histidine-tagged B Lymphocyte Stimulator are captured. Other cell lines that express B Lymphocyte Stimulator that might be useful for testing antibody binding to membrane-bound form of B Lymphocyte Stimulator include, K-562, HL-60 and THP-1 cells. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants) that bind to B Lymphocyte Stimulator on U937 membranes or to histidine-tagged B Lymphocyte Stimulator. In this assay, antibodies are added to 96 well plates coated with U937 membranes or histidine-tagged B Lymphocyte Stimulator and those antibodies or antibody fragments or variants that bind to the U937 membranes or histidine-tagged B Lymphocyte Stimulator are captured. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants thereof) that do not bind to biotinylated B Lymphocyte Stimulator (soluble B Lymphocyte Stimulator) but bind to membrane-bound B Lymphocyte Stimulator, such as, for example, that on membranes from U937 cells (see Example 2, *infra*). In these assays, soluble B Lymphocyte Stimulator (e.g., biotinylated B Lymphocyte Stimulator) and membrane-bound B Lymphocyte Stimulator (e.g., on U937 membranes) are incubated in separate samples with the same antibodies (or antibody fragments or variants) and those antibodies (or antibody fragments or variants) that do not bind to the soluble B Lymphocyte Stimulator (biotinylated B Lymphocyte Stimulator), but bind the membrane-bound B Lymphocyte Stimulator (e.g., on U937 membranes) are captured and identified. In other assays, antibodies are screened using ELISAs to determine which of the antibodies (or antibody fragments or variants) that bind to histidine-tagged B Lymphocyte Stimulator or membranes from U937 cells do not cross-react with APRIL, endokine-alpha, VEG1, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS (See Example 4, *infra*). ELISAs can also be used to determine which of the antibodies (or antibody fragments or variants) that bind to histidine-tagged B Lymphocyte Stimulator or membranes from U937 cells bind to B Lymphocyte Stimulator in the presence of TNF-alpha (see Example 4, *infra*). Antibodies or fragments or variants thereof that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator may also be tested for their affinity

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for histidine-tagged B Lymphocyte Stimulator using high-throughput BIAcore analysis (see Example 14, *infra*).

Additionally, antibodies of the invention may be screened against cells engineered to express an "uncleavable" form of B Lymphocyte Stimulator in order to determine their specificity for the membrane-bound form of B Lymphocyte Stimulator. Mutations in B Lymphocyte Stimulator which may achieve this result include, but are not limited to, the mutation or deletion of amino acid residues Lys-132 and/or Arg-133 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228. A typical mutagenesis might include mutation of one or both of residues Lys-132 or Arg-133 to alanine residues. Cells expressing such an "uncleavable" form of B Lymphocyte Stimulator provide a profound reagent to use in assaying the ability of antibodies to bind the membrane-bound form of B Lymphocyte Stimulator.

#### Selection and Screening for Antibodies that Immunospecifically Bind to Soluble and Membrane-Bound B Lymphocyte Stimulator

Antibodies of the invention (including scFvs and other molecules comprising, or alternately consisting of, antibody fragments or variants) may be screened in a variety of assays to identify those antibodies or antibody fragments or variants that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator. In one particular assay, antibodies that bind to immobilized B Lymphocyte Stimulator are captured. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants) that inhibit the binding of soluble B Lymphocyte Stimulator (i.e., soluble bio-B Lymphocyte Stimulator) to IM-9 cells as described supra. In other assays, antibodies are screened using ELISAs for those antibodies that bind to membranes from U937 cells. Additionally, further ELISA assays may be performed using techniques known in the art to determine which antibodies do not cross-react with APRIL, endokine-alpha, VEG1, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS, or those antibodies that bind to B Lymphocyte Stimulator in the presence of TNF-alpha (see Example 4 *infra*). Antibodies may be assayed in neutralization assays using techniques described herein or otherwise known in the art. Antibodies that immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator may also be tested for their affinity for B Lymphocyte Stimulator using high-throughput BIAcore analysis.

#### Antibody Conjugates

The present invention encompasses antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous polypeptide (or portion thereof, preferably at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids of the polypeptide) to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. For example, antibodies of the invention may be used to target heterologous polypeptides to particular cell types (e.g., cells of monocytic lineage and B-cells), either *in vitro* or *in vivo*, by fusing or conjugating the heterologous polypeptides to antibodies of the invention that are specific for particular cell surface antigens (e.g., membrane-bound B Lymphocyte Stimulator on cells of monocytic lineage) or which bind antigens that bind particular cell surface receptors (e.g., TACI and/or BCMA located on B cells). Antibodies fused or conjugated to



heterologous polypeptides may also be used in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/2 1232; EP 439,095; Naramura et al., *Immunol. Lett.* 39:91-99 (1994); U.S. Pat. No. 5,474,981; Gillies et al., *PNAS* 89:1428-1432 (1992); Fell et al., *J. Immunol.* 146:2446-2452 (1991), which are incorporated by reference in their entireties.

In one embodiment, a fusion protein comprises a polypeptide having an amino acid sequence of any one of the VH domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH CDR2s referred to in Table 1, and a heterologous polypeptide. In a preferred embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH CDR3s referred to in Table 1 (i.e., SEQ ID NOS:2129-3227), and a heterologous polypeptide.

In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR1s referred to in Table 1, and a heterologous polypeptide. In yet another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR2s referred to in Table 1, and a heterologous polypeptide. In a preferred embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR3s referred to in Table 1, and a heterologous polypeptide.

In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, and one or more VL domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein of the present invention comprises a polypeptide having the amino acid sequence of any one of the VH CDRs referred to in Table 1, and any one of the VL CDRs referred to in Table 1, and a heterologous polypeptide.

The present invention further includes compositions comprising, or alternatively consisting of, heterologous polypeptides fused or conjugated to antibody fragments. For example, the heterologous polypeptides may be fused or conjugated to a Fab fragment, Fd fragment, Fv fragment, F(ab)<sub>2</sub> fragment, or a portion thereof. Methods for fusing or conjugating polypeptides to antibody portions are known in the art. See, e.g., U.S. Pat. Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., *Proc. Natl. Acad. Sci. USA* 88:10535-10539 (1991); Zheng et al., *J. Immunol.* 154:5590-5600 (1995); and Vil et al., *Proc. Natl. Acad. Sci. USA* 89:11337-11341 (1992) (said references incorporated by reference in their entireties).

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), such methods can be used to generate antibodies with altered

activity (e.g., antibodies with higher affinities and lower dissociation rates). See, generally, U.S. Pat. Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., *Curr. Opin. Biotechnol.* 8:724-33 (1997); Hara-yama, *Trends Biotechnol.* 16(2):76-82 (1998); Hansson et al., *J. Mol. Biol.* 287:265-76 (1999); and Lorenz and Blasco, *Biotechniques* 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, polynucleotides encoding antibodies of the invention may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more portions of a polynucleotide encoding an antibody which portions immunospecifically bind to B Lymphocyte Stimulator may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Moreover, the antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), can be fused to marker sequences, such as a polypeptides to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine polypeptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, Calif., 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., *Cell* 37:767 (1984)) and the "flag" tag (DYKDDDDK, (SEQ ID No: 3238) Stratagene, La Jolla, Calif.).

The present invention further encompasses antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor or prognose the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include, but are not limited to, various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Pat. No. 4,741,990 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include, but are not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include, but are not limited to, streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include, but are not limited to, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes, but is not limited to, luminol; examples of bioluminescent materials include, but are not limited to, luciferase, luciferin, and aequorin; and examples

of suitable radioactive material include, but are not limited to, iodine ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115}\text{In}$ ,  $^{113}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{67}\text{Ga}$ ,  $^{68}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99\text{m}}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{143}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ,  $^{68}\text{Ge}$ ,  $^{57}\text{Co}$ ,  $^{65}\text{Zn}$ ,  $^{85}\text{Sr}$ ,  $^{32}\text{P}$ ,  $^{153}\text{Gd}$ ,  $^{169}\text{Yb}$ ,  $^{51}\text{Cr}$ ,  $^{54}\text{Mn}$ ,  $^{72}\text{Se}$ ,  $^{113}\text{Sn}$ , and  $^{117}\text{In}$ .

Further, an antibody of the invention (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof), may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,  $^{213}\text{Bi}$ . In specific embodiments, antibodies of the invention are attached to macrocyclic chelators useful for conjugating radiometal ions, including but not limited to,  $^{111}\text{In}$ ,  $^{177}\text{Lu}$ ,  $^{90}\text{Y}$ ,  $^{166}\text{Ho}$ , and  $^{153}\text{Sm}$ , to polypeptides. In preferred embodiments, the radiometal ion associated with the macrocyclic chelators attached to antibodies of the invention is  $^{111}\text{In}$ . In preferred embodiments, the radiometal ion associated with the macrocyclic chelators attached to antibodies of the invention is  $^{90}\text{Y}$ . In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In other specific embodiments, the DOTA is attached to the antibody of the invention via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art—see, for example, DeNardo et al., *Clin Cancer Res.* 4(10):2483-90, 1998; Peterson et al., *Bioconjug. Chem.* 10(4):553-7, 1999; and Zimmerman et al., *Nucl. Med. Biol.* 26(8):943-50, 1999 which are hereby incorporated by reference in their entirety.

A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells and includes such molecules as small molecule toxins and enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof. Examples include, but are not limited to, paclitaxel, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide (VP-16), teniposide, vincristine, vinblastine, colchicine, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrocortisterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, thymidine kinase, endonuclease, RNase, and puromycin and fragments, variants or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), antineoplastic agents (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthracycline (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine), imiprosulfan, piposulfan, benzodopa, carboplatin, metopredol, uredopa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide trimethylololmelamine, chlorophazine, chlorophosphamide, estramustine, ifosfamide, novembichin, pheusterine, prednimustine, trofosfamide, uracil mustard, chlorozotocin, fotemustine, nimustine, ranimustine, aclacinomysins, azaserine, cactinomycin, calicheamicin, carabacin, carminomycin, carzinophilin, chromomycins, detorubicin, 6-diazo-5-oxo-L-norleucine, epi-

bicin, esorubicin, idarubicin, marcellomycin, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfomycin, quetamycin, rodorubicin, streptonigrin, tubercidin, ubenun-xine, zinostatin, zorubicin, denopterin, pteropterin, trimetrexate, fludarabine, thiamiprine, acitabine, azacitidine, 6-azauridine, carmofur, didoxypyridine, doxilofuridine, enocitabine, flouxuridine, 5-FU, calusterone, dromostanolone propionate, epitiostanol, neupitostane, testosterone, aminoglutethimide, mitotane, trilostane, frolic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, amascrine, bestrabucil, bisantrene, edatraxate, defofamine, dermocolicine, diaziquone, elformethine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidamine, mitoguanzone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, PSKO, razoxane, sizofiran, spirogermanium, tenazotic acid, triaziquone, 2, 2', 2''-trichlorotriethylamine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobromol, gacytosine, arabinoside ("Ara-C"), taxoids, e.g. paclitaxel (TAXOL™), Bristol-Myers Squibb Oncology, Princeton, N.J.) doxetaxel (TAXOTERE™), Rhône-Poulenc Rorer, Antony, France), gemcitabine, ifosfamide, vinorelbine, navelbine, novatrone, teniposide, aminopterin, xeloda, idronatone, CPT-11, topoisomerase inhibitor RFS 2000, difluoromethylthine (DMFO), retinoic acid, esperamicin, capecitabine, and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4 hydroxytamoxifen, toxiolene, keoxifene, LY 117018, onapristone, toremifene (Fareston), and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin, and pharmaceutically acceptable salts, acids or derivatives of any of the above.

Techniques known in the art may be applied to label antibodies of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Pat. Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety) and direct coupling reactions (e.g., Bolton-Hunter and Chloramine-T reaction).

The antibodies of the invention which are conjugates can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, but are not limited to, for example, a toxin such as abrin, ricin A, alpha toxin, pseudomonas exotoxin, or diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (see, International Publication No. WO 97/33899), AIM II (see, International Publication No. WO 97/34911), Fas Ligand (Takahashi et al., *Int. Immunol.* 6:1567-1574 (1994)), VEGF (see, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiotensin or endothelin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-

6), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), or other growth factors.

Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polycrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating a therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985); and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

Alternatively, an antibody of the invention can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Pat. No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody of the invention (including an scFv or other molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

#### Use of Antibodies for Epitope Mapping

The present invention provides antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that can be used to identify epitopes of B Lymphocyte Stimulator. In particular, the antibodies of the present invention can be used to identify epitopes of human B Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or B Lymphocyte Stimulator expressed on human monocytes; murine B Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or B Lymphocyte Stimulator expressed on murine monocytes; rat B Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey B Lymphocyte Stimulator (e.g., the monkey B Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey B Lymphocyte Stimulator, or B Lymphocyte Stimulator expressed on monkey monocytes) using techniques described herein or otherwise known in the art. Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, *Proc. Natl. Acad. Sci. USA* 82:5131-5135 (1985), further described in U.S. Pat. No. 4,631,211.)

#### Diagnostic Uses of Antibodies

Labeled antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody frag-

ments or variants thereof) which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognosis, or monitor diseases and/or disorders associated with the aberrant expression and/or activity of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase or decrease in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of aberrant expression.

By "biological sample" is intended any fluids and/or cells obtained from an individual, body fluid, body tissue, body cell, cell line, tissue culture, or other source which may contain B Lymphocyte Stimulator protein or mRNA. Body fluids include, but are not limited to, sera, plasma, urine, synovial fluid, spinal fluid, saliva, and mucous. Tissues samples may be taken from virtually any tissue in the body. Tissue samples may also be obtained from autopsy material. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

The invention also provides for the detection of aberrant expression of B Lymphocyte Stimulator receptor comprising (a) assaying the expression of B Lymphocyte Stimulator receptor in a biological sample from an individual using one or more antibodies or fragments or variants thereof that immunospecifically binds only to soluble B Lymphocyte Stimulator, but does not inhibit B Lymphocyte Stimulator/B Lymphocyte Stimulator receptor binding. Such an antibody, by way of an example that is not to be construed as limiting, would be one that is able to capture a biotinylated B Lymphocyte Stimulator from solution (see Example 8), but that would not prevent B Lymphocyte Stimulator from binding to IM-9 cells (see Example 3), and (b) comparing the level of B Lymphocyte Stimulator receptor with a standard level of B Lymphocyte Stimulator receptor, e.g., in normal tissue or cell samples, whereby an increase or decrease in the assayed level of B Lymphocyte Stimulator receptor compared to the standard level of B Lymphocyte Stimulator receptor is indicative of aberrant expression.

Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognosis, or monitor autoimmune disorders and/or immunodeficiencies, and/or diseases or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase or decrease in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of an autoimmune disorder or disease and/or an immunodeficiency. In specific embodiments, an increase in the assayed level of B Lymphocyte

Stimulator is indicative of an autoimmune disorder or disease. In other specific embodiments, a decrease in the assayed level of B Lymphocyte Stimulator is indicative of an immunodeficiency.

Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to B Lymphocyte Stimulator but, do not inhibit B Lymphocyte Stimulator/B Lymphocyte Stimulator receptor binding can be used for diagnostic purposes to detect, diagnose, prognosis, or monitor autoimmune disorders and/or immunodeficiencies, and/or diseases or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator receptor comprising: (a) assaying the expression of B Lymphocyte Stimulator receptor in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator receptor with a standard level of B Lymphocyte Stimulator receptor, e.g., in normal biological samples, whereby an increase or decrease in the assayed level of B Lymphocyte Stimulator receptor compared to the standard level of B Lymphocyte Stimulator receptor is indicative of an autoimmune disorder or disease and/or an immunodeficiency. In specific embodiments, an increase in the assayed level of B Lymphocyte Stimulator receptor is indicative of an autoimmune disorder or disease. In other specific embodiments, a decrease in the assayed level of B Lymphocyte Stimulator receptor is indicative of an immunodeficiency.

Autoimmune disorders, diseases, or conditions that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmune cytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henoch-Schönlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, diabetes mellitus (e.g. Type I diabetes mellitus or insulin dependent diabetes mellitus), juvenile onset diabetes, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis, systemic lupus erythematosus, discoid lupus, Goodpasture's syndrome, Pemphigus, Receptor autoimmune diseases such as, for example, (a) Graves' Disease, (b) Myasthenia Gravis, and (c) insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, scleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia (Addison's disease), idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjögren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiomyopathy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders and other disorders such as inflammatory skin diseases including psoria-

sis and sclerosis, responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), respiratory distress syndrome (including adult respiratory distress syndrome, ARDS), meningitis, encephalitis, colitis, allergic conditions such as eczema and other conditions involving infiltration of T cells and chronic inflammatory responses, atherosclerosis, leukocyte adhesion deficiency, Reynaud's syndrome, and immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes typically found in tuberculosis, sarcoidosis, granulomatosis and diseases involving leukocyte diapedesis, central nervous system (CNS) inflammatory disorder, multiple organ injury syndrome, antigen-antibody complex mediated diseases, anti-glomerular basement membrane disease, Lambert-Eaton myasthenic syndrome, Behcet disease, giant cell arteritis, immune complex nephritis, IgA nephropathy, IgM polyneuropathies or autoimmune thrombocytopenia etc.

In specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies). In other specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypogammaglobulinemia (e.g., an immunodeficiency).

Immunodeficiencies that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated IgG, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia/aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nefzelof syndrome-combined immunodeficiency with IgG, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

Elevated levels of soluble B Lymphocyte Stimulator have been observed in the serum of patients with Systemic Lupus Erythematosus (SLE). In comparing the sera of 150 SLE patients with that of 38 control individuals, it was found that most of the SLE patients had more than 5 ng/ml of serum B Lymphocyte Stimulator, more than 30% of SLE patients had levels greater than 10 ng/ml, and approximately 10% of SLE patients had serum B Lymphocyte Stimulator levels greater than 20 ng/ml. In contrast, the majority of normal controls had B Lymphocyte Stimulator levels less than 5 ng/ml, and less than 10% had levels higher than 10 ng/ml. The elevated

levels of B Lymphocyte Stimulator protein in sera is present in the soluble form and has biologic activity as assayed by the ability to stimulate anti-IgM treated B cells in vitro. SLE patients with more than 15 ng/ml serum B Lymphocyte Stimulator were also found to have elevated levels of anti-dsDNA antibodies compared to both normal controls and SLE patients with less than 5 ng/ml of serum B Lymphocyte Stimulator. (unpublished data).

In addition the serum of two subgroups of patients which were positive for anti-nuclear antibodies (ANA+) but did not meet the formal requirements of the American College of Rheumatology (ACR) for classification of SLE were analyzed for B Lymphocyte Stimulator levels. The first subgroup of sera was ANA+ sera that came from patients who did not present with the clinical impression of SLE. This group had only slightly elevated levels of B Lymphocyte Stimulator (~9 ng/ml B Lymphocyte Stimulator). The second subgroup however, which was ANA+ sera from patients who presented with the clinical impression of SLE, had significantly increased B Lymphocyte Stimulator levels (~15 ng/ml). These results suggest that an elevated level of B Lymphocyte Stimulator precedes the formal fulfillment of the ACR criteria. The ACR criteria are described in Tan, E. M., et al, *Arthritis and Rheumatism* 25:1271-1277 (1982).

Thus in specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Systemic Lupus Erythematosus or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of SLE.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor IgA nephropathy or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of IgA nephropathy.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Sjögren's Syndrome or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator

compared to the standard level of B Lymphocyte Stimulator is indicative of Sjögren's Syndrome.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor HIV infection or conditions associated therewith (e.g. AIDS). The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of HIV infection.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Myasthenia Gravis or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of Myasthenia Gravis.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor idiopathic thrombocytopenic purpura (ITP) or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of idiopathic thrombocytopenic purpura (ITP).

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor hemolytic anemia or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of hemolytic anemia.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor thyroiditis or conditions associated therewith.

The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of thyroiditis.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Goodpasture's syndrome or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of Goodpasture's syndrome.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor multiple sclerosis or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of multiple sclerosis.

In additional embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Rheumatoid Arthritis. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample (e.g., serum and synovial fluid) of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of Rheumatoid arthritis.

In additional embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor an immune-based rheumatologic disease, (e.g., SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia.), Seronegative spondyloarthropathy (SpA), Polymyositis/dermatomyositis, Microscopic polyangiitis, Hepatitis C-associated arthritis, Takayasu's arteritis, and undifferentiated connective tissue disorder). The invention

provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample (e.g., serum and synovial fluid) of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of monitor an immune-based rheumatologic disease.

It has been observed, that serum B Lymphocyte Stimulator levels inversely correlate with nephrotic range proteinuria ( $>3$  gm proteinuria in a 24 hour urine collection) using a sample of 71 SLE patients ( $p=0.019$ ). Proteinuria was determined in 71 SLE patients within one month of phlebotomy for serum B Lymphocyte Stimulator determination. Serum B Lymphocyte Stimulator was classified as low, normal, or high based on the 5<sup>th</sup> through 95<sup>th</sup> percentiles for normal controls. Nephrotic-range proteinuria was inversely correlated with serum Neutrokin- $\alpha$  levels. Thus, in specific embodiments, serum levels of B Lymphocyte Stimulator (determined using one or more antibodies of the present invention) in individuals diagnosed with an immune based rheumatologic disease (e.g., SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia.), seronegative spondyloarthropathy (SpA), polymyositis/dermatomyositis, microscopic polyangiitis, hepatitis C-associated arthritis, Takayasu's arteritis, and undifferentiated connective tissue disorder) may be used to determine, diagnose, prognose, or monitor the severity of certain aspects or symptoms of the disease, such as nephrotic-range proteinuria.

In another specific embodiment, antibodies of the invention are used to diagnose, prognose, treat, or prevent conditions associated with COVID, including, but not limited to, conditions associated with acute and recurring infections (e.g., pneumonia, bronchitis, sinusitis, otitis media, sepsis, meningitis, septic arthritis, and osteomyelitis), chronic lung disease, autoimmunity, granulomatous disease, lymphoma, cancers (e.g., cancers of the breast, stomach, colon, mouth, prostate, lung, vagina, ovary, skin, and melanin forming cells (i.e. melanoma), inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, and ulcerative proctitis), malabsorption, Hodgkin's disease, and Waldenström's macroglobulinemia.

The invention provides a diagnostic assay for diagnosing or prognosing a disease or disorder, comprising: (a) assaying for the level of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard B Lymphocyte Stimulator level, e.g., in a biological sample from a patient without the disease or disorder, whereby an increase or decrease in the assayed B Lymphocyte Stimulator level compared to the standard level of B Lymphocyte Stimulator is indicative of a particular disease or disorder. With respect to cancer, the presence of a relatively high amount of B Lymphocyte Stimulator in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to

employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

In specific embodiments, the presence of a relatively high amount of membrane-bound B Lymphocyte Stimulator in a biological sample is indicative of monocytic cell related leukemias or lymphomas, such as, for example acute myelogenous leukemia and/or the severity thereof.

In other specific embodiments, the presence of a relatively high amount of B Lymphocyte Stimulator receptor in a biological sample (as determined using antibodies of the invention that bind to soluble B Lymphocyte Stimulator, but do not inhibit B Lymphocyte Stimulator/B Lymphocyte Stimulator receptor binding) is indicative of B cell related leukemias or lymphomas (e.g., chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, and Hodgkin's disease), and/or the severity thereof.

In specific embodiments, the invention provides a diagnostic assay for diagnosing or prognosing Systemic Lupus Erythematosus, comprising: (a) assaying for the level of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard B Lymphocyte Stimulator level, e.g., in a biological sample from a patient without Systemic Lupus Erythematosus, whereby an increase in the assayed B Lymphocyte Stimulator level compared to the standard level of B Lymphocyte Stimulator is indicative of Systemic Lupus Erythematosus.

In specific embodiments, the invention provides a diagnostic assay for diagnosing or prognosing a Rheumatoid Arthritis, comprising: (a) assaying for the level of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard B Lymphocyte Stimulator level, e.g., in a biological sample from a patient without Rheumatoid Arthritis, whereby an increase or decrease in the assayed B Lymphocyte Stimulator level compared to the standard level of B Lymphocyte Stimulator is indicative of Rheumatoid Arthritis.

The invention provides a diagnostic assay for diagnosing or prognosing a disease or disorder, comprising: (a) assaying for the level of B Lymphocyte Stimulator receptor in cells or a tissue sample of an individual using one or more antibodies of the invention that immunospecifically binds only to soluble B Lymphocyte Stimulator, but does not neutralize B Lymphocyte Stimulator/B Lymphocyte Stimulator receptor binding; and (b) comparing the level of B Lymphocyte Stimulator receptor with a standard B Lymphocyte Stimulator receptor level, e.g., in a tissue sample from a patient without the disease or disorder, whereby an increase or decrease in the assayed B Lymphocyte Stimulator receptor level compared to the standard level of B Lymphocyte Stimulator receptor is indicative of a particular disease or disorder. With respect to cancer, the presence of a relatively high amount of B Lymphocyte Stimulator receptor in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) can be used to assay protein levels in a biological sample using classical immunohistological methods as described herein or as known to those of skill in the art (e.g., see Jalkanen, et al., *J. Cell. Biol.* 101:976-985 (1985); Jalkanen, et al., *J. Cell. Biol.* 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, alkaline phosphatase, and horseradish peroxidase; radioisotopes, such as iodine ( $^{121}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{111}\text{In}$ ,  $^{113}\text{In}$ ,  $^{115}\text{mIn}$ ), technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99\text{m}}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{188}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ , and  $^{97}\text{Ru}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parentally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically binds to B Lymphocyte Stimulator; b) waiting for a time interval following the administering for permitting the labeled antibody to preferentially concentrate at sites in the subject where B Lymphocyte Stimulator is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled antibody in the subject, such that detection of labeled antibody or fragment thereof above the background level and above or below the level observed in a person without the disease or disorder indicates that the subject has a particular disease or disorder associated with aberrant expression of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of  $^{99}\text{Tc}$ . The labeled antibody will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S. W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and their Fragments." (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S. W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In

another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disorder, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as positron emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Pat. No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

#### Immunophenotyping

The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be utilized for immunophenotyping of cell lines and biological samples by their B Lymphocyte Stimulator expression or B Lymphocyte Stimulator receptor expression. Various techniques can be utilized using antibodies, fragments, or variants of the invention to screen for cellular populations (i.e., immune cells, particularly monocytic cells or B-cells) expressing B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor, and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (see, e.g., U.S. Pat. No. 5,985,660; and Morrison et al., *Cell*, 96:737-49 (1999)).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e., minimal residual disease (MRD) in acute leukemic patients) and "non-sell" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

In one embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) are used to identify cells of monocytic or B cell origin.

#### Therapeutic Uses of Antibodies

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention and nucleic acids encoding antibodies (and anti-idiotypic antibodies) of the invention as described

herein. The antibodies of the invention can be used to treat, ameliorate or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant B Lymphocyte Stimulator expression and/or activity or aberrant B Lymphocyte Stimulator receptor expression and/or activity includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that function as agonists or antagonists of B Lymphocyte Stimulator, preferably of B Lymphocyte Stimulator-induced signal transduction, can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, lack of B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or lack of B Lymphocyte Stimulator receptor function. For example, antibodies of the invention which disrupt the interaction between B Lymphocyte Stimulator and its receptor may be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, excessive B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or excessive of B Lymphocyte Stimulator receptor function. Antibodies of the invention which do not prevent B Lymphocyte Stimulator from binding its receptor but inhibit or downregulate B Lymphocyte Stimulator-induced signal transduction can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator function, excessive B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or excessive B Lymphocyte Stimulator receptor function. In particular, antibodies of the present invention which prevent B Lymphocyte Stimulator-induced signal transduction by specifically recognizing the unbound B Lymphocyte Stimulator, receptor-bound B Lymphocyte Stimulator or both unbound and receptor-bound B Lymphocyte Stimulator can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, excessive B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or excessive B Lymphocyte Stimulator receptor function. The ability of an antibody of the invention to inhibit or downregulate B Lymphocyte Stimulator-induced signal transduction may be determined by techniques described herein or otherwise known in the art. For example, B Lymphocyte Stimulator-induced receptor activation and the activation of signaling molecules can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or a signaling molecule by immunoprecipitation followed by western blot analysis (for example, as described herein).

In a specific embodiment, an antibody of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that inhibits or downregulates B Lymphocyte Stimulator activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%,



at least 25%, at least 20%, or at least 10% relative to B Lymphocyte Stimulator activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, excessive B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or excessive B Lymphocyte Stimulator receptor function. In another embodiment, a combination of antibodies, a combination of antibody fragments, a combination of antibody variants, or a combination of antibodies, antibody fragments, and/or variants that inhibit or downregulate B Lymphocyte Stimulator activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to B Lymphocyte Stimulator activity in absence of said antibodies, antibody fragments, and/or antibody variants are administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, excessive B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or excessive B Lymphocyte Stimulator receptor function.

Further, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which activate B Lymphocyte Stimulator-induced signal transduction can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, lack of B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or lack of B Lymphocyte Stimulator receptor function. These antibodies may potentiate or activate either all or a subset of the biological activities of B Lymphocyte Stimulator-mediated receptor activation, for example, by inducing multimerization of B Lymphocyte Stimulator and/or multimerization of the receptor. The antibodies of the invention may be administered with or without being pre-complexed with B Lymphocyte Stimulator. In a specific embodiment, an antibody of the present invention that increases B Lymphocyte Stimulator activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% relative to B Lymphocyte Stimulator activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, lack of B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or lack of B Lymphocyte Stimulator receptor function. In another embodiment, a combination of antibodies, a combination of antibody fragments, a combination of antibody variants, or a combination of antibodies, antibody fragments and/or antibody variants that increase B Lymphocyte Stimulator activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% relative to B Lymphocyte Stimulator activity in absence of the said antibodies or antibody fragments and/or antibody variants is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or lack of B Lymphocyte Stimulator function or aberrant B

Lymphocyte Stimulator receptor expression or lack of B Lymphocyte Stimulator receptor function.

One or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator may be used locally or systemically in the body as a therapeutic. The antibodies of this invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may also be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy, anti-tumor agents, anti-angiogenesis and anti-inflammatory agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments, or variants, (e.g., derivatives), or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator, or polynucleotides encoding antibodies that immunospecifically bind to B Lymphocyte Stimulator, for both immunoassays directed to and therapy of disorders related to B Lymphocyte Stimulator polynucleotides or polypeptides, including fragments thereof. Such antibodies will preferably have an affinity for B Lymphocyte Stimulator and/or B Lymphocyte Stimulator fragments. Preferred binding affinities include those with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M, or  $10^{-5}$  M. More preferably, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M, or  $10^{-8}$  M. Even more preferably, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with a dissociation constant or  $K_D$  less than or equal to  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M. The invention encompasses antibodies that bind B Lymphocyte Stimulator polypeptides with a dissociation constant or  $K_D$  that is within any one of the ranges that are between each of the individual recited values.

In a preferred embodiment, antibodies of the invention neutralize B Lymphocyte Stimulator activity. In another preferred embodiment, antibodies of the invention inhibit B cell proliferation.

In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of the soluble form of B Lymphocyte Stimulator to a B Lymphocyte Stimulator receptor. In another preferred embodiment antibodies of the invention inhibit or reduce B cell proliferation induced by the soluble form of B Lymphocyte Stimulator. In another preferred embodiment anti-

bodies of the invention inhibit or reduce immunoglobulin production induced by the soluble form of B Lymphocyte Stimulator.

In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of membrane-bound B Lymphocyte Stimulator to a B Lymphocyte Stimulator receptor. In another preferred embodiment, antibodies of the invention inhibit or reduce B cell proliferation induced by the membrane-bound form of B Lymphocyte Stimulator. In another preferred embodiment, antibodies of the invention inhibit or reduce immunoglobulin production induced by the membrane bound form of B Lymphocyte Stimulator.

In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of both the soluble and membrane-bound forms of B Lymphocyte Stimulator to a B Lymphocyte Stimulator receptor. In another preferred embodiment, antibodies of the invention inhibit or reduce B cell proliferation induced by either or both forms of B Lymphocyte Stimulator. In another preferred embodiment, antibodies of the invention inhibit or reduce immunoglobulin production induced by either or both forms of B Lymphocyte Stimulator.

In one embodiment, the invention provides a method of delivering antibody conjugates of the invention to targeted cells, such as, for example, monocytic cells expressing the membrane-bound form of B Lymphocyte Stimulator, or B cells expressing a B Lymphocyte Stimulator receptor.

In one embodiment, the invention provides a method for the specific delivery of antibodies and antibody conjugates of the invention to cells by administering molecules of the invention that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs). In a specific embodiment, the invention provides a method for the specific destruction of cells of monocytic lineage (e.g., monocytic cell related leukemias or lymphomas, such as, for example acute myelogenous leukemia) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs) that immunospecifically bind the membrane-bound form of B Lymphocyte Stimulator. In another specific embodiment, the invention provides a method for the specific destruction of cells of B cell lineage (e.g., B cell related leukemias or lymphomas (e.g., chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, and Hodgkin's disease) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs) that bind soluble B Lymphocyte Stimulator, but do not inhibit B Lymphocyte Stimulator binding to a B Lymphocyte Stimulator receptor on B cells.

In another preferred embodiment antibodies of the invention (including antibody fragments and variants) promote or enhance B cell proliferation induced by the soluble form of

B Lymphocyte Stimulator. In another preferred embodiment, antibodies of the invention (including antibody fragments and variants) promote or enhance B cell proliferation induced by the membrane or soluble form of APRIL. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhance immunoglobulin production induced by the soluble form of B Lymphocyte Stimulator. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhance immunoglobulin production induced by the membrane bound or soluble form of APRIL. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhance immunoglobulin production in response to T cell dependent immunogens. In another preferred embodiment antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance immunoglobulin production in response to T cell independent immunogens.

In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate immune disorders. Immune disorders include, but are not limited to, autoimmune disorders (e.g., arthritis, graft rejection, Hashimoto's thyroiditis, insulins-dependent diabetes, lupus, idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis), elective IgA deficiency, ataxia-telangiectasia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, idiopathic hyper-eosinophilic syndrome, monocytic leukemoid reaction, monocytic leukocytosis, monocytic leukopenia, monocytopenia, monocytosis, and graft or transplant rejection.

As discussed herein, antibodies and antibody compositions of the invention, may be used to treat, prevent, ameliorate, diagnose or prognose various immune system-related disorders and/or conditions associated with these disorders, in mammals, preferably humans. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of antibody and antibody compositions of the invention that can inhibit an immune response, particularly the proliferation of B cells and/or the production of immunoglobulins, may be an effective therapy in treating and/or preventing autoimmune disorders. Thus, in preferred embodiments, antibodies and antibody compositions of the invention are used to treat, prevent, ameliorate, diagnose and/or prognose an autoimmune disorder, or condition(s) associated with such disorder.

Autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmune cytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henoch-Schoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre

Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

Additional autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis) (often characterized, e.g., by cell-mediated and humoral thyroid cytotoxicity), systemic lupus erythematosus (often characterized, e.g., by circulating and locally generated immune complexes), discoid lupus, Goodpasture's syndrome (often characterized, e.g., by anti-basement membrane antibodies), Pemphigus (often characterized, e.g., by epidermal acantholytic antibodies), Receptor autoimmunities such as, for example, (a) Graves' Disease (often characterized, e.g., by TSH receptor antibodies), (b) Myasthenia Gravis (often characterized, e.g., by acetylcholine receptor antibodies), and (c) insulin resistance (often characterized, e.g., by insulin receptor antibodies), autoimmune hemolytic anemia (often characterized, e.g., by phagocytosis of antibody-sensitized RBCs), autoimmune thrombocytopenic purpura (often characterized, e.g., by phagocytosis of antibody-sensitized platelets).

Additional autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, rheumatoid arthritis (often characterized, e.g., by immune complexes in joints), scleroderma with anti-collagen antibodies (often characterized, e.g., by nuclear and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis/dermatomyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes) such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjögren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies), chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondrial antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), inflammatory myopathies, and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

In a preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, a member of the group: autoimmune hemolytic anemia, as primary glomerulonephritis, IgA glomerulonephritis, Goodpasture's syndrome, idiopathic thrombocytopenia, Multiple Sclerosis, Myasthenia Gravis, Pemphigus, polymyositis/dermatomyositis, relapsing polychondritis, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, Uveitis, vasculitis, and primary biliary cirrhosis.

In another preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, an immune based-rheumatologic disease, such as, for example, SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia.), Seronegative spondyloarthropathy (SpA), polymyositis/dermatomyositis, microscopic polyangiitis, hepatitis C-associated arthritis, Takayasu's arteritis, and undifferentiated connective tissue disorder.

In a specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, rheumatoid arthritis and/or medical conditions associated therewith.

For example, an antibody, or antibodies, of the present invention are used to treat patients with clinical diagnosis of rheumatoid arthritis (RA). The patient treated preferably will not have a B cell malignancy. Moreover, the patient is optionally further treated with any one or more agents employed for treating RA such as salicylate; nonsteroidal anti-inflammatory drugs such as indomethacin, phenylbutazone, phenylacetic acid derivatives (e.g. ibuprofen and fenoprofen), naphthalene acetic acids (naproxen), pyrrolizone (ketoprofen), indoleacetic acids (sulindac), halogenated anthranilic acid (mefenamic acid sodium), piroxicam, zomepirac and diflunisal; antimalarials such as chloroquine; gold salts; penicillamine; or immunosuppressive agents such as methotrexate or corticosteroids in dosages known for such drugs or reduced dosages. Preferably however, the patient is only treated with an antibody, or antibodies, of the present invention. Antibodies of the present invention are administered to the RA patient according to a dosing schedule as described infra, which may be readily determined by one of ordinary skill in the art. The primary response is determined by the Paulus index (Paulus et al. *Arthritis Rheum.* 33:477-484 (1990)), i.e. improvement in morning stiffness, number of painful and inflamed joints, erythrocyte sedimentation (ESR), and at least a 2-point improvement on a 5-point scale of disease severity assessed by patient and by physician. Administration of an antibody, or antibodies, of the present invention will alleviate one or more of the symptoms of RA in the patient treated as described above.

In a specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, lupus and/or medical conditions associated therewith. Lupus-associated conditions that may be treated, prevented, ameliorated, prognosed and/or diagnosed with the antibodies and antibody compositions of the invention include, but are not limited to, hematologic disorders (e.g., hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia), immunologic disorders (e.g., anti-DNA antibodies, and anti-Sm antibodies), rashes, photosensitivity, oral ulcers, arthritis, fever, fatigue, weight loss, serositis (e.g., pleuritis (pleurisy)), renal disorders (e.g., nephritis), renal disorder-

ders (e.g., seizures, peripheral neuropathy, CNS related disorders), gastrointestinal disorders, Raynaud phenomenon, and pericarditis. In a preferred embodiment, therapeutic and pharmaceutical compositions of the invention are used to treat, prevent, ameliorate, diagnose, or prognose, renal disorders associated with systemic lupus erythematosus. In a most preferred embodiment, therapeutic and pharmaceutical compositions of the invention are used to treat, prevent, ameliorate, diagnose, or prognose, nephritis associated with systemic lupus erythematosus. In another most preferred embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate lupus or glomerular nephritis.

In a further specific embodiment, antibodies of the invention are used to treat, inhibit, prognose, diagnose or prevent hemolytic anemia. For example, patients diagnosed with autoimmune hemolytic anemia (AIHA), e.g., cryoglobulinemia or Coombs positive anemia, are treated with an antibody, or antibodies, of the present invention. AIHA is an acquired hemolytic anemia due to auto-antibodies that react with the patient's red blood cells. The patient treated preferably will not have a B cell malignancy. Further adjunct therapies (such as glucocorticoids, prednisone, azathioprine, cyclophosphamide, vinca-laden platelets or Danazol) may be combined with the antibody therapy, but preferably the patient is treated with an antibody, or antibodies, of the present invention as a single-agent throughout the course of therapy. Antibodies of the present invention are administered to the hemolytic anemia patient according to a dosing schedule as described infra, which may be readily determined by one of ordinary skill in the art. Overall response rate is determined based upon an improvement in blood counts, decreased requirement for transfusions, improved hemoglobin levels and/or a decrease in the evidence of hemolysis as determined by standard chemical parameters. Administration of an antibody, or antibodies of the present invention will improve any one or more of the symptoms of hemolytic anemia in the patient treated as described above. For example, the patient treated as described above will show an increase in hemoglobin and an improvement in chemical parameters of hemolysis or return to normal as measured by serum lactic dehydrogenase and/or bilirubin.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Sjögren's Syndrome and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, HIV infection and/or medical conditions associated therewith (e.g. AIDS).

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Myasthenia gravis and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, IgA nephropathy and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, hemolytic anemia and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, thyroiditis and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Goodpasture's Syndrome and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, multiple sclerosis and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, chronic lymphocytic leukemia (CLL) and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, multiple myeloma and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Non-Hodgkin's lymphoma and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Hodgkin's disease and/or medical conditions associated therewith.

In another specific embodiment, antibodies of the invention are used to treat, inhibit, prognose, diagnose or prevent adult immune thrombocytopenic purpura. Adult immune thrombocytopenic purpura (ITP) is a relatively rare hematologic disorder that constitutes the most common of the immune-mediated cytopenias. The disease typically presents with severe thrombocytopenia that may be associated with acute hemorrhage in the presence of normal to increased megakaryocytes in the bone marrow. Most patients with ITP have an IgG antibody directed against target antigens on the outer surface of the platelet membrane, resulting in platelet sequestration in the spleen and accelerated reticuloendothelial destruction of platelets (Bussell, J. B. *Hematol. Oncol. Clin. North Am.* (4):179 (1990)). A number of therapeutic interventions have been shown to be effective in the treatment of ITP. Steroids are generally considered first-line therapy, after which most patients are candidates for intravenous immunoglobulin (IVIg), splenectomy, or other medical therapies including vincristine or immunosuppressive/cytotoxic agents. Up to 80% of patients with ITP initially respond to a course of steroids, but far fewer have complete and lasting remissions. Splenectomy has been recommended as standard second-line therapy for steroid failures, and leads to prolonged remission in nearly 60% of cases yet may result in reduced immunity to infection. Splenectomy is a major surgical procedure that may be associated with substantial morbidity (15%) and mortality (2%). IVIG has also been used as second line medical therapy, although only a small proportion of adult patients with ITP achieve remission. Therapeutic options that would interfere with the production of autoantibodies by activated B cells without the associated morbidities that occur with corticosteroids and/or splenectomy would provide an important treatment approach for a proportion of patients with ITP. Patients with clinical diagnosis of ITP are treated with an antibody, or antibodies of the present invention, optionally in combination with steroid therapy. The patient treated will not have a B cell malignancy. Antibodies of the present invention are administered to the RA patient according to a dosing schedule as described infra, which may be readily

determined by one of ordinary skill in the art. Overall patient response rate is determined based upon a platelet count determined on two consecutive occasions two weeks apart following treatments as described above. See, George et al. "Idiopathic Thrombocytopenic Purpura: A Practice Guideline Developed by Explicit Methods for The American Society of Hematology", Blood 88:3-40 (1996), expressly incorporated herein by reference.

In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate an IgE-mediated allergic reaction or histamine-mediated allergic reaction. Examples of allergic reactions include, but are not limited to, asthma, rhinitis, eczema, chronic urticaria, and atopic dermatitis. In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent, or ameliorate anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility. In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate or modulate inflammation or an inflammatory disorder. Examples of chronic and acute inflammatory disorders that may be treated prevented or ameliorated with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, chronic prostatitis, granulomatous prostatitis and malacoplakia, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, Crohn's disease, inflammatory bowel disease, chronic and acute inflammatory pulmonary diseases, bacterial infection, psoriasis, septicemia, cerebral malaria, arthritis, gastroenteritis, and glomerular nephritis.

In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate ischemia and arteriosclerosis. Examples of such disorders include, but are not limited to, reperfusion damage (e.g., in the heart and/or brain) and cardiac hypertrophy.

Therapeutic or pharmaceutical compositions of the invention, may also be administered to modulate blood clotting and to treat or prevent blood clotting disorders, such as, for example, antibody-mediated thrombosis (i.e., antiphospholipid antibody syndrome (APS)). For example, therapeutic or pharmaceutical compositions of the invention, may inhibit the proliferation and differentiation of cells involved in producing antithrombotic antibodies. These compositions of the invention can be used to treat, prevent, ameliorate, diagnose, and/or prognose thrombotic related events including, but not limited to, stroke (and recurrent stroke), heart attack, deep vein thrombosis, pulmonary embolism, myocardial infarction, coronary artery disease (e.g., antibody-mediated coronary artery disease), thrombosis, graft reocclusion following cardiovascular surgery (e.g., coronary arterial bypass grafts, recurrent fetal loss, and recurrent cardiovascular thromboembolic events).

Therapeutic or pharmaceutical compositions of the invention, may also be administered to treat, prevent, or ameliorate organ rejection or graft-versus-host disease (GVHD) and/or conditions associated therewith. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of antibodies of the invention, that

inhibit an immune response, may be an effective therapy in preventing organ rejection or GVHD.

In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate a disease or disorder diseases associated with increased apoptosis including, but not limited to, AIDS, neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration), myelodysplastic syndromes (such as aplastic anemia), ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia. In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate bone marrow failure, for example, aplastic anemia and myelodysplastic syndrome.

In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate growth, progression, and/or metastases of malignancies and proliferative disorders associated with increased cell survival, or the inhibition of apoptosis. Examples of such disorders, include, but are not limited to, leukemia (e.g., acute leukemia such as acute lymphocytic leukemia and acute myelocytic leukemia), neoplasms, tumors (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chondroma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma), heavy chain disease, metastases, or any disease or disorder characterized by uncontrolled cell growth.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used to treat or prevent a disorder characterized by hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies).

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used to treat or prevent a disorder characterized by deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, therapeutic or pharmaceutical compositions of the invention may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchi-

titis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or *pneumocystis carinii*.

Therapeutic or pharmaceutical compositions of the invention of the invention thereof, may be used to diagnose, prognose, treat or prevent one or more of the following diseases or disorders, or conditions associated therewith: primary immunodeficiencies, immune-mediated thrombocytopenia, Kawasaki syndrome, bone marrow transplant (e.g., recent bone marrow transplant in adults or children), chronic B-cell lymphocytic leukemia, HIV infection (e.g., adult or pediatric HIV infection), chronic inflammatory demyelinating polyneuropathy, and post-transfusion purpura.

Additionally, therapeutic or pharmaceutical compositions of the invention may be used to diagnose, prognose, treat or prevent one or more of the following diseases, disorders, or conditions associated therewith, Guillain-Barre syndrome, anemia (e.g., anemia associated with parvovirus B19, patients with stable multiple myeloma who are at high risk for infection (e.g., recurrent infection), autoimmune hemolytic anemia (e.g., warm-type autoimmune hemolytic anemia), thrombocytopenia (e.g., neonatal thrombocytopenia), and immune-mediated neutropenia), transplantation (e.g., cytomegalovirus (CMV)-negative recipients of CMV-positive organs), hypogammaglobulinemia (e.g., hypogammaglobulinemic neonates with risk factor for infection or morbidity), epilepsy (e.g., intractable epilepsy), systemic vasculitic syndromes, myasthenia gravis (e.g., decompensation in myasthenia gravis), dermatomyositis, and polymyositis.

Additional preferred embodiments of the invention include, but are not limited to, the use of therapeutic or pharmaceutical compositions of the invention in the following applications:

Administration to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response. In a specific nonexclusive embodiment, therapeutic or pharmaceutical compositions of the invention are administered to boost the immune system to produce increased quantities of IgG. In another specific nonexclusive embodiment, antibodies of the are administered to boost the immune system to produce increased quantities of IgA. In another specific nonexclusive embodiment antibodies of the invention are administered to boost the immune system to produce increased quantities of IgM.

Administration to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO/98/24893, WO/96/34096, WO/96/33735, and WO/91/0741).

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a vaccine adjuvant that enhances immune responsiveness to specific antigen. In a specific embodiment, the vaccine is an antibody described herein. In another specific embodiment, the vaccine adjuvant is a polynucleotide described herein (e.g., an antibody polynucleotide genetic vaccine adjuvant). As discussed herein, therapeutic or pharmaceutical compositions of the

invention may be administered using techniques known in the art, including but not limited to, liposomal delivery, recombinant vector delivery, injection of naked DNA, and gene gun delivery.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance tumor-specific immune responses.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include, but are not limited to, virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, Respiratory syncytial virus, Dengue, Rotavirus, Japanese B encephalitis, Influenza A and B, Parainfluenza, Measles, Cytomegalovirus, Rabies, Junin, Chikungunya, Rift Valley fever, Herpes simplex, and yellow fever. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to the HIV gp120 antigen.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, Group B *streptococcus*, *Shigella* spp., Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, *Borrelia burgdorferi*, and *Plasmodium* (malaria).

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to *Plasmodium* (malaria).

In a specific embodiment, compositions of the invention may be administered to patients as vaccine adjuvants. In a further specific embodiment, compositions of the invention may be administered as vaccine adjuvants to patients suffering from an immune-deficiency. In a further specific

embodiment, compositions of the invention may be administered as vaccine adjuvants to patients suffering from HIV.

In a specific embodiment, compositions of the invention may be used to increase or enhance antigen-specific antibody responses to standard and experimental vaccines. In a specific embodiment, compositions of the invention may be used to enhance seroconversion in patients treated with standard and experimental vaccines. In another specific embodiment, compositions of the invention may be used to increase the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination.

In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance antigen-specific antibody responses to standard and experimental vaccines by regulating binding of the soluble form of B Lymphocyte Stimulator to a B Lymphocyte Stimulator receptor (e.g., BCMA and TACI). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance antigen-specific antibody responses to standard and experimental vaccines by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance seroconversion in patients treated with standard and experimental vaccines by regulating binding of the soluble form of B Lymphocyte Stimulator to B Lymphocyte Stimulator receptor (e.g., BCMA and TACI). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance seroconversion in patients treated with standard and experimental vaccines by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination by regulating binding of the soluble form of B Lymphocyte Stimulator to a B Lymphocyte Stimulator receptor (e.g., BCMA and TACI). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a stimulator of B cell responsiveness to pathogens.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to induce higher affinity antibodies.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to increase serum immunoglobulin concentrations.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to accelerate recovery of immunocompromised individuals.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among aged populations.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy. B cell immunodeficiencies that may be ameliorated or treated by administering the antibodies and/or compositions of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia/aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

In a specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate selective IgA deficiency.

In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate ataxia-telangiectasia.

In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate common variable immunodeficiency.

In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate X-linked agammaglobulinemia.

In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate severe combined immunodeficiency (SCID).

In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate Wiskott-Aldrich syndrome.

In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate X-linked Ig deficiency with hyper IgM.

As an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering antibodies and/or compositions of the invention include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency that may be ameliorated or treated by administering antibodies and/or compositions of the invention include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, recovery from surgery.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a regulator of antigen presentation by monocytes, dendritic cells, T cells and/or B-cells. In one embodiment, antibody polypeptides or polynucleotides enhance antigen presentation or antagonize antigen presentation *in vitro* or *in vivo*. Moreover, in related embodiments, this enhancement or antagonization of antigen presentation may be useful in anti-tumor treatment or to modulate the immune system.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a mediator of mucosal immune responses. The expression of B Lymphocyte Stimulator on monocytes, the expression of B Lymphocyte Stimulator receptor on B cells, and the responsiveness of B cells to B Lymphocyte Stimulator suggests that it may be involved in exchange of signals between B cells and monocytes or their differentiated progeny. This activity is in many ways analogous to the CD40-CD154 signalling between B cells and T cells. Anti-B Lymphocyte Stimulator antibodies and compositions of the invention may therefore be good regulators of T cell independent immune responses to environmental pathogens. In particular, the unconventional B cell populations (CD5+) that are associated with mucosal sites and responsible for much of the innate immunity in humans may respond to antibodies or compositions of the invention thereby enhancing or inhibiting individual's immune status.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly, their susceptibility profile would likely change.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a monocyte cell specific binding protein to which specific activators or

inhibitors of cell growth may be attached. The result would be to focus the activity of such activators or inhibitors onto normal, diseased, or neoplastic B cell populations.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a B cell binding protein to which specific activators or inhibitors of cell growth may be attached. The result would be to focus the activity of such activators or inhibitors onto normal, diseased, or neoplastic B cell populations.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of detecting monocytic cells by virtue of its specificity. This application may require labeling the protein with biotin or other agents (e.g., as described herein) to afford a means of detection.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of detecting B-lineage cells by virtue of its specificity. This application may require labeling the protein with biotin or other agents (e.g., as described herein) to afford a means of detection.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable immunodeficiency.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as part of a monocyte selection device the function of which is to isolate monocytes from a heterogeneous mixture of cell types. Antibodies of the invention could be coupled to a solid support to which monocytes would then specifically bind. Unbound cells would be washed out and the bound cells subsequently eluted. A non-limiting use of this selection would be to allow purging of tumor cells from, for example, bone marrow or peripheral blood prior to transplant.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as part of a B cell selection device the function of which is to isolate B cells from a heterogeneous mixture of cell types. Antibodies of the invention (that do not inhibit B Lymphocyte Stimulator/B Lymphocyte Stimulator Receptor interaction) binding soluble B Lymphocyte Stimulator could be coupled to a solid support to which B cells would then specifically bind. Unbound cells would be washed out and the bound cells subsequently eluted. A non-limiting use of this selection would be to allow purging of tumor cells from, for example, bone marrow or peripheral blood prior to transplant.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence such as observed among SCID patients.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an antigen for the generation of antibodies to inhibit or enhance B Lymphocyte Stimulator mediated responses.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as *Leishmania*.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as pretreatment of



bone marrow samples prior to transplant. Such treatment would increase B cell representation and thus accelerate recovery.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of regulating secreted cytokines that are elicited by B Lymphocyte Stimulator and/or B Lymphocyte Stimulator receptor.

Antibody polypeptides or polynucleotides of the invention may be used to modulate IgE concentrations in vitro or in vivo.

Additionally, antibody polypeptides or polynucleotides of the invention may be used to treat, prevent, and/or diagnose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema.

In a specific embodiment, antibody polypeptides or polynucleotides of the invention, are administered to treat, prevent, diagnose, and/or ameliorate selective IgA deficiency.

In another specific embodiment antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate ataxia-telangiectasia.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate common variable immunodeficiency.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked agammaglobulinemia.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate severe combined immunodeficiency (SCID).

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate Wiskott-Aldrich syndrome.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked Ig deficiency with hyper IgM. In a specific embodiment antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked Ig deficiency with hyper IgM.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, and/or diagnose chronic myelogenous leukemia, acute myelogenous leukemia, leukemia, histiocytic leukemia, monocytic leukemia (e.g., acute monocytic leukemia), leukemic reticulosis, Shilling Type monocytic leukemia, and/or other leukemias derived from monocytes and/or monocytic cells and/or tissues.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate monocytic leukemoid reaction, as seen, for example, with tuberculosis.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate monocytic leukocytosis, monocytic leukopenia, monocytopenia, and/or monocytosis.

In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, detect, and/or diagnose monocytic disorders and/or diseases, and/or conditions associated therewith.

In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, detect, and/or diagnose primary B lymphocyte disorders and/or diseases, and/or conditions associated therewith. In one embodiment, such primary B lymphocyte disorders, diseases, and/or conditions are characterized by a complete or partial loss of humoral immunity. Primary B lymphocyte disorders, diseases, and/or conditions associated therewith that are characterized by a complete or partial loss of humoral immunity and that may be prevented, treated, detected and/or diagnosed with compositions of the invention include, but are not limited to, X-Linked Agammaglobulinemia (XLA), severe combined immunodeficiency disease (SCID), and selective IgA deficiency.

In a preferred embodiment antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose diseases or disorders affecting or conditions associated with any one or more of the various mucous membranes of the body. Such diseases or disorders include, but are not limited to, for example, mucositis, mucoclasia, mucoclitosis, mucocutaneous leishmaniasis (such as, for example, American leishmaniasis, leishmaniasis americana, nasopharyngeal leishmaniasis, and New World leishmaniasis), mucocutaneous lymph node syndrome (for example, Kawasaki disease), mucoenteritis, mucopidermoid carcinoma, mucopidermoid tumor, mucopithelial dysplasia, mucoid adenocarcinoma, mucoid degeneration, myxoid degeneration; myxomatous degeneration; myxomatosis, mucoid medial degeneration (for example, cystic medial necrosis), mucopolipidosis (including, for example, mucopolipidosis I, mucopolipidosis II, mucopolipidosis III, and mucopolipidosis IV), mucopolisidosis, mucocutaneous enteritis, mucoenteritis, mucopolysaccharidosis (such as, for example, type I mucopolysaccharidosis (i.e., Hurler's syndrome), type IS mucopolysaccharidosis (i.e., Scheie's syndrome or type V mucopolysaccharidosis), type II mucopolysaccharidosis (i.e., Hunter's syndrome), type III mucopolysaccharidosis (i.e., Sanfilippo's syndrome), type IV mucopolysaccharidosis (i.e., Morquio's syndrome), type VI mucopolysaccharidosis (i.e., Maroteaux-Lamy syndrome), type VII mucopolysaccharidosis (i.e., mucopolysaccharidosis due to beta-glucuronidase deficiency), and mucosulfatidosis), mucopolysacchariduria, mucopurulent conjunctivitis, mucopus, mucormycosis (i.e., zygomycosis), mucosal disease (i.e., bovine virus diarrhoea), mucous colitis (such as, for example, mucoclitosis and myxomebranous colitis), and mucoviscidosis (such as, for example, cystic fibrosis, cystic fibrosis of the pancreas, Clarke-Hadfield syndrome, fibrocystic disease of the pancreas, mucoviscidosis, and viscidosis). In a highly preferred embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose mucositis, especially as associated with chemotherapy.

In a preferred embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose diseases or disorders affecting or conditions associated with sinusitis.

An additional condition, disease or symptom that can be treated, prevented, and/or diagnosed by antibody polypeptides or polynucleotides of the invention is osteomyelitis.

An additional condition, disease or symptom that can be treated, prevented, and/or diagnosed by antibody polypeptides or polynucleotides of the invention is endocarditis.

All of the above described applications as they may apply to veterinary medicine.

Antibody polypeptides or polynucleotides of the invention may be used to treat, prevent, and/or diagnose diseases

and disorders of the pulmonary system (e.g., bronchi such as, for example, sinopulmonary and bronchial infections and conditions associated with such diseases and disorders and other respiratory diseases and disorders. In specific embodiments, such diseases and disorders include, but are not limited to, bronchial adenoma, bronchial asthma, pneumonia (such as, e.g., bronchial pneumonia, bronchopneumonia, and tuberculous bronchopneumonia), chronic obstructive pulmonary disease (COPD), bronchial polyps, bronchiectasia (such as, e.g., bronchiectasia sicca, cylindrical bronchiectasis, and saccular bronchiectasis), bronchiolar adenocarcinoma, bronchiolar carcinoma, bronchiolitis (such as, e.g., exudative bronchiolitis, bronchiolitis fibrosa obliterans, and proliferative bronchiolitis), bronchiolo-alveolar carcinoma, bronchitic asthma, bronchitis (such as, e.g., asthmatic bronchitis, Castellani's bronchitis, chronic bronchitis, croupous bronchitis, fibrinous bronchitis, hemorrhagic bronchitis, infectious avian bronchitis, obliterative bronchitis, plastic bronchitis, pseudomembranous bronchitis, putrid bronchitis, and verminous bronchitis), bronchocentric granulomatosis, bronchoedema, bronchosophageal fistula, bronchogenic carcinoma, bronchogenic cyst, bronchiolitis, bronchomalacia, bronchomyiasis (such as, e.g., bronchopulmonary aspergillosis), bronchopulmonary spirochetosis, hemorrhagic bronchitis, bronchorrhea, bronchospasm, bronchostasis, bronchostenosis, Biot's respiration, bronchial respiration, Kussmaul respiration, Kussmaul-Kien respiration, respiratory acidosis, respiratory alkalosis, respiratory distress syndrome of the newborn, respiratory insufficiency, respiratory scleroma, respiratory syncytial virus, and the like.

In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose chronic obstructive pulmonary disease (COPD).

In another embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose fibroses and conditions associated with fibroses, including, but not limited to, cystic fibrosis (including such fibroses as cystic fibrosis of the pancreas, Clarke-Hadfield syndrome, fibrocystic disease of the pancreas, mucoviscidosis, and viscidosis), endomyocardial fibrosis, idiopathic retroperitoneal fibrosis, leptomeningeal fibrosis, mediastinal fibrosis, nodular subepidermal fibrosis, pericentral fibrosis, perimuscular fibrosis, pipestem fibrosis, replacement fibrosis, subadventitial fibrosis, and Symmers' clay pipestem fibrosis.

In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate infectious diseases. Infectious diseases include diseases associated with yeast, fungal, viral and bacterial infections. Viruses causing viral infections which can be treated or prevented in accordance with this invention include, but are not limited to, retroviruses (e.g., human T-cell lymphotropic virus (HTLV) types I and II and human immunodeficiency virus (HIV)), herpes viruses (e.g., herpes simplex virus (HSV) types I and II, Epstein-Barr virus, HHV6-HHV8, and cytomegalovirus), arenaviruses (e.g., lassa fever virus), paramyxoviruses (e.g., morbillivirus virus, human respiratory syncytial virus, mumps, and pneumovirus), adenoviruses, bunyaviruses (e.g., hantavirus), coronaviruses, filoviruses (e.g., Ebola virus), flaviviruses (e.g., hepatitis C virus (HCV), yellow fever virus, and Japanese encephalitis virus), hepadnaviruses (e.g., hepatitis B virus (HBV)), orthomyxoviruses (e.g., influenza viruses A, B and C), papovaviruses (e.g., papillomaviruses), picornaviruses (e.g., rhinoviruses, enteroviruses and hepatitis A viruses), poxviruses, reoviruses (e.g., rotaviruses), togaviruses (e.g.,

rubella virus), rhabdoviruses (e.g., rabies virus). Microbial pathogens causing bacterial infections include, but are not limited to, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Neisseria gonorrhoea*, *Neisseria meningitidis*, *Corynebacterium diphtheriae*, *Clostridium botulinum*, *Clostridium perfringens*, *Clostridium tetani*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Klebsiella rhinoscleromatis*, *Staphylococcus aureus*, *Vibrio cholerae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Campylobacter* (*Vibrio*) *fetus*, *Campylobacter jejuni*, *Aeromonas hydrophila*, *Bacillus cereus*, *Edwardsiella tarda*, *Yersinia enterocolitica*, *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Salmonella typhimurium*, *Treponema pallidum*, *Treponema pertenue*, *Treponema caratense*, *Borrelia vincentii*, *Borrelia burgdorferi*, *Leptospira icterohaemorrhagiae*, *Mycobacterium tuberculosis*, *Toxoplasma gondii*, *Pneumocystis carinii*, *Francisella tularensis*, *Brucella abortus*, *Brucella suis*, *Brucella melitensis*, *Mycoplasma* spp., *Rickettsia prowazekii*, *Rickettsia tsutsugumushi*, *Chlamydia* spp., and *Helicobacter pylori*.

#### Gene Therapy

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of B Lymphocyte Stimulator and/or its receptor, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., *Clinical Pharmacy* 12:488-505 (1993); Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, *TIBTECH* 11(5): 155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); and Kriegler, *Gene Transfer and Expression*, A Laboratory Manual, Stockton Press, NY (1990).

In a preferred aspect, a composition of the invention comprises, or alternatively consists of, nucleic acids encoding an antibody, said nucleic acids being part of an expression vector that expresses the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acids have promoters, preferably heterologous promoters, operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342: 435-438 (1989). In specific embodiments, the expressed antibody molecule is an scFv; alternatively, the nucleic acid

sequences include sequences encoding both the heavy and light chains, or fragments or variants thereof, of an antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids *in vitro*, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or *ex vivo* gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Pat. No. 4,980, 286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, *J. Biol. Chem.* 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188; WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435-438 (1989)).

In a specific embodiment, viral vectors that contain nucleic acid sequences encoding an antibody of the invention or fragments or variants thereof are used. For example, a retroviral vector can be used (see Miller et al., *Meth. Enzymol.* 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdr* 1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Klein et al., *Blood* 83:1467-1473 (1994); Salmon and Gunzburg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable

of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Pat. No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, *Meth. Enzymol.* 217:599-618 (1993); Cohen et al., *Meth. Enzymol.* 217:618-644 (1993); *Clin. Pharma. Ther.* 29:69-92m (1985)) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody or fragment thereof are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered *in vivo* for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can

be isolated and maintained *in vitro* can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

#### Demonstration of Therapeutic or Prophylactic Utility of a Composition

The compounds of the invention are preferably tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays which can be used to determine whether administration of a specific antibody or composition of the present invention is indicated, include *in vitro* cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered an antibody or composition of the present invention, and the effect of such an antibody or composition of the present invention upon the tissue sample is observed. In various specific embodiments, *in vitro* assays can be carried out with representative cells of cell types involved in a patient's disorder, to determine if an antibody or composition of the present invention has a desired effect upon such cell types. Preferably, the antibodies or compositions of the invention are also tested *in vitro* assays and animal model systems prior to administration to humans.

Antibodies or compositions of the present invention for use in therapy can be tested for their toxicity in suitable animal model systems, including but not limited to rats, mice, chicken, cows, monkeys, and rabbits. For *in vivo* testing of an antibody or composition's toxicity any animal model system known in the art may be used.

Efficacy in treating or preventing viral infection may be demonstrated by detecting the ability of an antibody or composition of the invention to inhibit the replication of the virus, to inhibit transmission or prevent the virus from establishing itself in its host, or to prevent, ameliorate or alleviate the symptoms of disease a progression. The treatment is considered therapeutic if there is, for example, a reduction in viral load, amelioration of one or more symptoms, or a decrease in mortality and/or morbidity following administration of an antibody or composition of the invention.

Antibodies or compositions of the invention can be tested for the ability to induce the expression of cytokines such as IFN- $\gamma$ , by contacting cells, preferably human cells, with an antibody or composition of the invention or a control antibody or control composition and determining the ability of the antibody or composition of the invention to induce one or more cytokines. Techniques known to those of skill in the art can be used to measure the level of expression of cytokines. For example, the level of expression of cytokines can be measured by analyzing the level of RNA of cytokines by, for example, RT-PCR and Northern blot analysis, and by analyzing the level of cytokines by, for example, immunoprecipitation followed by western blot analysis and ELISA. In a preferred embodiment, a compound of the invention is tested for its ability to induce the expression of IFN- $\gamma$ .

Antibodies or compositions of the invention can be tested for their ability to modulate the biological activity of

immune cells by contacting immune cells, preferably human immune cells (e.g., T-cells, B-cells, and Natural Killer cells), with an antibody or composition of the invention or a control compound and determining the ability of the antibody or composition of the invention to modulate (i.e., increase or decrease) the biological activity of immune cells. The ability of an antibody or composition of the invention to modulate the biological activity of immune cells can be assessed by detecting the expression of antigens, detecting the proliferation of immune cells (i.e., B-cell proliferation), detecting the activation of signaling molecules, detecting the effector function of immune cells, or detecting the differentiation of immune cells. Techniques known to those of skill in the art can be used for measuring these activities. For example, cellular proliferation can be assayed by <sup>3</sup>H-thymidine incorporation assays and trypan blue cell counts. Antigen expression can be assayed, for example, by immunoassays including, but not limited to, competitive and non-competitive assay systems using techniques such as western blots, immunohistochemistry radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immuno-radiometric assays, fluorescent immunoassays, protein A immunoassays and FACS analysis. The activation of signaling molecules can be assayed, for example, by kinase assays and electrophoretic shift assays (EMSA). In a preferred embodiment, the ability of an antibody or composition of the invention to induce B-cell proliferation is measured. In another preferred embodiment, the ability of an antibody or composition of the invention to modulate immunoglobulin expression is measured.

Antibodies or compositions of the invention can be tested for their ability to reduce tumor formation *in vitro*, *ex vivo* and *in vivo* assays. Antibodies or compositions of the invention can also be tested for their ability to inhibit viral replication or reduce viral load *in vitro* and *in vivo* assays. Antibodies or compositions of the invention can also be tested for their ability to reduce bacterial numbers *in vitro* and *in vivo* assays known to those of skill in the art. Antibodies or compositions of the invention can also be tested for their ability to alleviate of one or more symptoms associated with cancer, an immune disorder (e.g., an inflammatory disease), a neurological disorder or an infectious disease. Antibodies or compositions of the invention can also be tested for their ability to decrease the time course of the infectious disease. Further, antibodies or compositions of the invention can be tested for their ability to increase the survival period of animals suffering from disease or disorder, including cancer, an immune disorder or an infectious disease. Techniques known to those of skill in the art can be used to analyze the function of the antibodies or compositions of the invention *in vivo*.

#### Therapeutic/Prophylactic Compositions and Administration

The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of antibody (or fragment or variant thereof) or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, an antibody or fragment or variant thereof is substantially purified (i.e., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to, animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably a human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

Various delivery systems are known and can be used to administer antibody or fragment or variant thereof of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody or antibody fragment, receptor-mediated endocytosis (see, e.g., Wu and Wu, *J. Biol. Chem.* 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as dialysis membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, *ibid.*, pp. 3 17-327; see generally *ibid.*).

In yet another embodiment, the composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Rev. Biomed. Eng.* 14:20 1 (1987); Buchwald et al., *Surgery* 88:507 (1980); Sandek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Press, Boca Raton, Fla. (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); see also Levy et al., *Science* 228:190 (1985); During et al., *Ann. Neurol.* 25:35 1 (1989); Howard et al., *J. Neurosurg.* 7 1:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

In a specific embodiment where the composition of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Pat. No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see e.g., Joliet et al., *Proc. Natl. Acad. Sci. USA* 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of an antibody or a fragment thereof, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will contain a therapeutically effective amount of the antibody or fragment thereof, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized

powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the composition of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of therapeutic or pharmaceutical compositions of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

The antibodies and antibody compositions of the invention may be administered alone or in combination with other adjuvants. Adjuvants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmuoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with alum. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, Adju Vax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, *Haemophilus influenzae* B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow

fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis, and/or PNEUMOVAX-23™. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In another specific embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated therewith. In one embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose any Gram positive bacterial infection and/or any disease, disorder, and/or condition associated therewith. In another embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with one or more members of the genus *Enterococcus* and/or the genus *Streptococcus*. In another embodiment, antibody and antibody compositions of the invention are used in any combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with one or more members of the Group B streptococci. In another embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with *Streptococcus pneumoniae*.

The antibody and antibody compositions of the invention may be administered alone or in combination with other therapeutic agents, including but not limited to, chemotherapeutic agents, antibiotics, antivirals, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents and cytokines. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In one embodiment, the antibody and antibody compositions of the invention are administered in combination with other members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, soluble forms of TNF- $\alpha$ , lymphotoxin- $\alpha$  (LT- $\alpha$ , also known as TNF- $\beta$ ), LT- $\beta$  (found in complex heterotrimer LT- $\alpha$ - $\beta$ 2), OPG, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), TRAIL, AIM-II (International Publication No. WO 97/34911), APRIL (J. Exp. Med. 188(6):1185-1190 (1998)), endokine- $\alpha$  (International Publication No. WO 98/07880), Neutrokin- $\alpha$  (International Application Publication No. WO 98/18921), OPG, OX40, and nerve

growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-1BB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with CD40 ligand (CD40L), a soluble form of CD40L (e.g., AVREND™), biologically active fragments, variants, or derivatives of CD40L, anti-CD40L antibodies (e.g., agonistic or antagonistic antibodies), and/or anti-CD40 antibodies (e.g., agonistic or antagonistic antibodies).

In an additional embodiment, the antibody and antibody compositions of the invention are administered alone or in combination with an anti-angiogenic agent(s). Anti-angiogenic agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, Md.), TROP-1 (Boston Life Sciences, Boston, Mass.), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGF, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin

derivatives (prepared from queen crab shells), (Murata et al., *Cancer Res.* 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP-PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dihydroxyproline, Thiazoprine, alpha, alpha-dipyrrolyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2 (3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., *J. Bio. Chem.* 267:17321-17326, 1992); Chymostatin (Tomkinson et al., *Biochem J.* 286:475-480, 1992); Cyclodextrin Tetradecanate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., *Nature* 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, *J. Clin. Invest.* 79:1440-1446, 1987); anticollagenase-serum; alpha-2-antiplasmin (Holmes et al., *J. Biol. Chem.* 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthranilic acid disodium or "CCA"; (Takeuchi et al., *Agents Actions* 36:312-316, 1992); and metalloproteinase inhibitors such as BB94.

Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, N.J.); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J. Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J. Clin. Invest.* 103:47-54 (1999)); carboxyaminoimidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, Md.); Conbratstatin A-4 (CA4P) (OXIGENE, Boston, Mass.); Squallamine (Magainin Pharmaceuticals, Plymouth Meeting, Pa.); TNP-470, (Tap Pharmaceuticals, Deerfield, Ill.); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Eudostatin; Flvopridol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; P1-88; P1-nomastat (AG-3340) Purylin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

Anti-angiogenic agents that may be administered in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, AG-3340 (Agouron, La Jolla, Calif.), BAY-12-9566 (Bayer, West Haven, Conn.), BMS-275291 (Bristol Myers Squibb, Princeton, N.J.), CGS-27032A (Novartis, East Hanover, N.J.), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, EMD-121974 (Merck & Co., Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, Calif./Medimmune, Gaithersburg, Md.). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combi-

nation with the antibody and antibody compositions of the invention include, but are not limited to, Angiozyme (Ri-bozyme, Boulder, Colo.), Anti-VEGF antibody (Genentech, S. San Francisco, Calif.), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, Calif.), SU-5416 (Sugen/Pharmacia Upjohn, Bridgewater, N.J.), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, Wash.), Interferon-alpha, IL-12 (Roche, Nutley, N.J.), and Pentosan polysulfate (Georgetown University, Washington, D.C.).

In particular embodiments, the use of antibody and antibody compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

In a particular embodiment, the use of antibody and antibody compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of antibody and antibody compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

In another embodiment, antibody and antibody compositions of the invention are administered in combination with an anticoagulant. Anticoagulants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, heparin, warfarin, and aspirin. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin and/or warfarin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with warfarin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with warfarin and aspirin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin and aspirin.

In another embodiment, antibody and antibody compositions of the invention are administered in combination with an agent that suppresses the production of anticardiolipin antibodies. In specific embodiments, the polynucleotides of the invention are administered in combination with an agent that blocks and/or reduces the ability of anticardiolipin antibodies to bind phospholipid-binding plasma protein beta 2-glycoprotein I (b2GPI).

In certain embodiments, antibody and antibody compositions of the invention are administered in combination with antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPVIR™ (laminivudine/3TC), and COMBIVIR™ (zidovudine/laminivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the antibody and antibody

compositions of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavir-dine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, CRIVIR™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with antibody and antibody compositions of the invention to treat, prevent, and/or diagnose AIDS and/or to treat, prevent, and/or diagnose HIV infection.

In other embodiments, antibody and antibody compositions of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMY-CIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, antibody and antibody compositions of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOX-AZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZI-NAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Mycobacterium avium* complex infection. In another specific embodi-ment, antibody and antibody compositions of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat, prevent, and/or diagnose an opportu-nistic *Mycobacterium tuberculosis* infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with GANCI-CLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat, prevent, and/or diagnose an opportu-nistic cytomegalovirus infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with FLUCONA-ZOLE™, ITRACONAZOLE™, and/or KETOCONA-ZOLE™ to prophylactically treat, prevent, and/or diagnose an opportunistic fungal infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat, prevent, and/or diagnose an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with



LEUCOVORIN™ and/or NUPOGENT™ to prophylactically treat, prevent, and/or diagnose an opportunistic bacterial infection.

In a further embodiment, the antibody and antibody compositions of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In a further embodiment, the antibody and antibody compositions of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, amoxicillin, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

Conventional nonspecific immunosuppressive agents, that may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs cyclophosphamide, cyclophosphamide IV, methylprednisolone, prednisolone, azathioprine, FK-506, 15-deoxyspergulin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

In specific embodiments, antibody and antibody compositions of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucorticosteroids, and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with steroid therapy. Steroids that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, oral corticosteroids, prednisone, and methylprednisolone (e.g., IV methylprednisolone). In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with prednisone. In a further specific embodiment, the antibody and antibody compositions of the invention are administered in combination with prednisone and an immunosuppressive agent. Immunosuppressive agents that may be administered with the antibody and antibody compositions of the invention and prednisone are those described herein, and include, but are not limited to, azathioprine, cyclophosphamide, and cyclophosphamide IV. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with methylprednisolone. In a further specific embodiment, the antibody and antibody compositions of the invention are administered in combination with methylprednisolone and an immunosuppressive agent. Immunosuppressive agents that may be administered with the antibody and antibody compositions of the invention and methylprednisolone are those described herein, and include, but are not limited to, azathioprine, cyclophosphamide, and cyclophosphamide IV.

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial. Antimalarials that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, hydroxychloroquine, chloroquine, and/or quinine.

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an NSAID.

In a nonexclusive embodiment, the antibody and antibody compositions of the invention are administered in combination with one, two, three, four, five, ten, or more of the following drugs: NR1-101 (Hoechst Marion Roussel), diclofenac (Dimethaid), oxaprozin potassium (Monsanto), mecamermin (Chiron), T-614 (Toyama), pemetrexed disodium (Eli Lilly), atreleuton (Abbott), valdecoxib (Monsanto), etelnac (Byk Gulden), campath, AGM-1470 (Takeda), CDP-571 (Celltech Chiroscience), CM-101 (CarboMed), ML-3000 (Merckle), CB-2431 (KS Biomedix), CBF-BS2 (KS Biomedix), IL-1Ra gene therapy (Valentis), JTE-522 (Japan Tobacco), peficitaxel (Angiotech), DW-1661C (Dong Wha), darbifutolene mesylate (Warner-Lambert), soluble TNF receptor 1 (synergen; Amgen), IPR-6001 (Institute for Pharmaceutical Research), trocade (Hoffman-La Roche), EF-5 (Scotia Pharmaceuticals), BILL-284 (Boehringer Ingelheim), BILL-1149 (Boehringer Ingelheim), Lcuko Vax (Inflammatics), MK-663 (Merck), ST-1482 (Sigma-Tau), and butixocort propionate (WarnerLambert).

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with one, two, three, four, five or more of the following drugs: methotrexate, sulfasalazine, sodium aurothiomalate, auranoftin, cyclosporine, penicillamine, azathioprine, an antimalarial drug (e.g., as described herein), cyclophosphamide, chlorambucil, gold, ENBRELM™ (Etanercept), anti-TNF antibody, LJP 394 (La Jolla Pharmaceutical Company, San Diego, Calif.) and prednisolone.

In a more preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial, methotrexate, anti-TNF antibody, ENBRELM™ and/or sulfasalazine. In one embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with anti-TNF antibody. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate and anti-TNF antibody. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with sulfasalazine. In another specific embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate, anti-TNF antibody, and sulfasalazine. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBRELM™. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBRELM™ and methotrexate. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBRELM™, methotrexate and sulfasalazine. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBRELM™, methotrexate and sulfasalazine. In other embodiments, one or more antimalarials is combined with one of the above-recited combinations. In a specific embodiment, the antibody and antibody compositions of the inven-

tion are administered in combination with an antimalarial (e.g., hydroxychloroquine), ENBREL™, methotrexate and sulfasalazine. In another specific embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial (e.g., hydroxychloroquine), sulfasalazine, anti-TNF antibody, and methotrexate.

In an additional embodiment, antibody and antibody compositions of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the antibody and antibody compositions of the invention include, but not limited to, GAMMART™, IVEEGAM™, SANDOGLLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

CD40 ligand (CD40L), a soluble form of CD40L (e.g., AVREND™), biologically active fragments, variants, or derivatives of CD40L, anti-CD40L antibodies (e.g., agonistic or antagonistic antibodies), and/or anti-CD40 antibodies (e.g., agonistic or antagonistic antibodies).

In an additional embodiment, the antibody and antibody compositions of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, aryl-lactic acid derivatives, arylbutyric acid derivatives, aryl-carboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides,  $\alpha$ -acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzylamine, buclonine, difenpiramide, ditalol, emorfonazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paronyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

In another embodiment, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, antitubercular derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antineoplastic agents (e.g., tamoxifen); antineoplastic agents (e.g., fluorouracil, 5-FU, methotrexate, flouxidine, interferon  $\alpha$ -2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diposphate, chlorotrianisene, and testosterone); nitrogen mustard derivatives (e.g., mephalen, chlorambucil, mechlorethamine (nitrogen mustard) and thiopeta); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, antibody and antibody compositions of the invention are administered in combination

with Rituximab. In a further embodiment, antibody and antibody compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of the components of CHOP.

In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with cytokines. Cytokines that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, GM-CSF, G-CSF, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, anti-CD40, CD40L, IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$ , TNF- $\alpha$ , and TNF- $\beta$ . In preferred embodiments, antibody and antibody compositions of the invention are administered with B Lymphocyte Stimulator (e.g., amino acids 134-285 of SEQ ID NO:3228). In another embodiment, antibody and antibody compositions of the invention may be administered with any interleukin, including, but not limited to, IL-1  $\alpha$ , IL-1  $\beta$ , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, and IL-22. In preferred embodiments, the antibody and antibody compositions of the invention are administered in combination with IL-4 and IL-10.

In one embodiment, the antibody and antibody compositions of the invention are administered in combination with one or more chemokines. In specific embodiments, the antibody and antibody compositions of the invention are administered in combination with an  $\alpha$ (CXC) chemokine selected from the group consisting of gamma-interferon inducible protein-10 (iIP-10), interleukin-8 (IL-8), platelet factor-4 (PF4), neutrophil activating protein (NAP-2), GRO- $\alpha$ , GRO- $\beta$ , GRO- $\gamma$ , neutrophil-activating peptide (ENA-78), granulocyte chemoattractant protein-2 (GCP-2), and stromal cell-derived factor-1 (SDF-1, or pre-B cell stimulatory factor (PBSF)); and/or a  $\beta$ (CC) chemokine selected from the group consisting of: RANTES (regulated on activation, normal T expressed and secreted), macrophage inflammatory protein-1 alpha (MIP-1 $\alpha$ ), macrophage inflammatory protein-1 beta (MIP-1 $\beta$ ), monocyte chemoattractant protein-1 (MCP-1), monocyte chemoattractant protein-2 (MCP-2), monocyte chemoattractant protein-3 (MCP-3), monocyte chemoattractant protein-4 (MCP-4), macrophage inflammatory protein-1 gamma (MIP-1 $\gamma$ ), macrophage inflammatory protein-3 alpha (MIP-3 $\alpha$ ), macrophage inflammatory protein-3 beta (MIP-3 $\beta$ ), macrophage inflammatory protein-4 (MIP-4/DC-CK-1/ PARC), eotaxin, Exodust, and I-309; and/or the  $\gamma$ (C) chemokine, lymphotactin.

In another embodiment, the antibody and antibody compositions of the invention are administered with chemokine beta-8, chemokine beta-1, and/or macrophage inflammatory protein-4. In a preferred embodiment, the antibody and antibody compositions of the invention are administered with chemokine beta-8.

In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with an IL-4 antagonist. IL-4 antagonists that may be administered with the antibody and antibody compositions of the invention include, but are not limited to: soluble IL-4 receptor polypeptides, multimeric forms of soluble IL-4 receptor polypeptides; anti-IL-4 receptor antibodies that bind the IL-4 receptor without transducing the biological signal elicited by IL-4; anti-IL-4 antibodies that block binding of IL-4 to one or more IL-4 receptors, and mutants of IL-4 that bind IL-4 receptors but do not transduce the biological signal elicited by IL-4. Preferably, the antibodies employed according to this method are monoclonal antibodies (including antibody fragments, such as, for example, those described herein).

The invention also encompasses combining the polynucleotides and/or polypeptides of the invention (and/or agonists or antagonists thereof) with other proposed or conventional hematopoietic therapies. Thus, for example, the polynucleotides and/or polypeptides of the invention (and/or agonists or antagonists thereof) can be combined with compounds that singly exhibit erythropoietic stimulatory effects, such as erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, and triiodothyronine. Also encompassed are combinations of the antibody and antibody compositions of the invention with compounds generally used to treat aplastic anemia, such as, for example, methenolene, stanozolol, and nandrolone; to treat iron-deficiency anemia, such as, for example, iron preparations; to treat malignant anemia, such as, for example, vitamin B<sub>12</sub> and/or folic acid; and to treat hemolytic anemia, such as, for example, adrenocortical steroids, e.g., corticoids. See e.g., Resegotti et al., *Panninierva Medica*, 23:243-248 (1981); Kurtz, *FEBS Letters*, 144:105-108 (1982); McGonigle et al., *Kidney Int.*, 25:437-444 (1984); and Pavlovic-Kanter, *Expt. Hematol.*, 8(suppl. 8) 283-291 (1980), the contents of each of which are hereby incorporated by reference in their entirety.

Compounds that enhance the effects of or synergize with erythropoietin are also useful as adjuvants herein, and include but are not limited to, adrenergic agonists, thyroid hormones, androgens, hepatic erythropoietic factors, erythrotropins, and erythropoiesis. See for e.g., Dunn, "Current Concepts in Erythropoiesis", John Wiley and Sons (Chichester, England, 1983); Kalmanni, *Kidney Int.*, 22:383-391 (1982); Shahidi, *New Eng. J. Med.*, 289:72-80 (1973); Urabe et al., *J. Exp. Med.*, 149:1314-1325 (1979); Billat et al., *Expt. Hematol.*, 10:133-140 (1982); Naughton et al., *Acta Haemat.*, 69:171-179 (1983); Cognote et al. in abstract 364, *Proceedings 7th Intl. Cong. of Endocrinology* (Quebec City, Quebec, Jul. 1-7, 1984); and Rothman et al., 1982, *J. Surg. Oncol.*, 20:105-108 (1982). Methods for stimulating hematopoiesis comprise administering a hematopoietically effective amount (i.e., an amount which effects the formation of blood cells) of a pharmaceutical composition containing polynucleotides and/or polypeptides of the invention (and/or agonists or antagonists thereof) to a patient. The polynucleotides and/or polypeptides of the invention and/or agonists or antagonists thereof is administered to the patient by any suitable technique, including but not limited to, parenteral, sublingual, topical, intrapulmonary and intranasal, and those techniques further discussed herein. The pharmaceutical composition optionally contains one or more members of the group consisting of erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, triiodothyronine, methenolene, stanozolol, and nandrolone, iron preparations, vitamin B<sub>12</sub>, folic acid and/or adrenocortical steroids.

In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIN™) and NEUPOGEN™ (FILGRASITIN™).

In an additional embodiment, the antibody and antibody compositions of the invention are administered in combina-

tion with fibroblast growth factors. Fibroblast growth factors that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

Additionally, the antibody and antibody compositions of the invention may be administered alone or in combination with other therapeutic regimens, including but not limited to, radiation therapy. Such combinatorial therapy may be administered sequentially and/or concomitantly.

#### Kits

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In an alternative embodiment, a kit comprises an antibody fragment that immunospecifically binds to B Lymphocyte Stimulator. In a specific embodiment, the kits of the present invention contain a substantially isolated B Lymphocyte Stimulator polypeptide as a control. Preferably, the kits of the present invention further comprise a control antibody which does not react with B Lymphocyte Stimulator. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to B Lymphocyte Stimulator (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized B Lymphocyte Stimulator. The B Lymphocyte Stimulator provided in the kit may also be attached to a solid support. In a more specific embodiment the detecting means of the above-described kit includes a solid support to which B Lymphocyte Stimulator is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to B Lymphocyte Stimulator can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with B Lymphocyte Stimulator, and means for detecting the binding of B Lymphocyte Stimulator to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound B Lymphocyte

Stimulator obtained by the methods of the present invention. After B Lymphocyte Stimulator binds to a specific antibody, the unbound serum components are removed by washing, reporter-labeled anti-human antibody is added, unbound anti-human antibody is removed by washing, and a reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-B Lymphocyte Stimulator antibody on the solid support. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate.

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant B Lymphocyte Stimulator, and a reporter-labeled anti-human antibody for detecting surface-bound anti-B Lymphocyte Stimulator antibody.

In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908.

In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880.

In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128.

In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1 to 1562.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128, and in which said antibody or fragment thereof immunospecifically binds to the membrane-bound form of B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH

domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880, and in which said antibody or fragment thereof immunospecifically binds to the soluble form of B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128, and in which said antibody or fragment thereof immunospecifically binds to the membrane-bound form of B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880, and in which said antibody or fragment thereof immunospecifically binds to the soluble form of B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, and in which said VL and said VH domains are derived from the same scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator.

In specific embodiments, the antibody or fragment thereof of the invention is a whole immunoglobulin molecule.

In specific embodiments, the antibody or fragment thereof of the invention is a Fab fragment.

In specific embodiments, the antibody or fragment thereof of the invention is a Fv fragment.

In specific embodiments, the present invention encompasses a chimeric protein comprising the antibody or fragment thereof of the invention covalently linked to a heterologous polypeptide.

In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which

type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and wherein each type of antibody or fragment thereof further comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 3129 to 3227.

In specific embodiments, the present invention encompasses a panel of two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NO: 1 to 2128.

In specific embodiments, the present invention encompasses a panel of two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NO: 1 to 2128.

In specific embodiments, the present invention encompasses a panel of two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NO: 1 to 2128 and wherein each type of antibody or fragment further comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses a panel of two or more antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VHCDR3 from a different scFv having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

In specific embodiments, the antibodies or fragments thereof of the antibody panel of the invention, are each in a well of a 96 well plate.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 1908, wherein the antibody of fragment thereof immunospecifically binds the membrane-bound form of B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1569, wherein said antibody of fragment thereof immunospecifically binds the soluble form of B Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or

fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128, wherein the antibody of fragment thereof immunospecifically binds the membrane-bound form of B Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880, wherein said antibody of fragment thereof immunospecifically binds the soluble form of B Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors.

Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and in which said VL domain and said VH domain are derived from the same scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VHCDR3 from an scFv having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-de-

scribed nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VH domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VH domain encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a CDR encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a CDR from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a CDR encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a CDR from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VH CDR3 encoded by a nucleotide sequence that hybridizes

under stringent conditions to a nucleotide sequence encoding a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VH CDR3 encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

In specific embodiments, the present invention provides a method for detecting of aberrant expression of B Lymphocyte Stimulator, comprising:

assaying the level of B Lymphocyte Stimulator expression in cells or a tissue sample of an individual using one or more antibodies or fragments or variants thereof that immunospecifically bind B Lymphocyte Stimulator; and

comparing the level of B Lymphocyte Stimulator assayed in the cells or a tissue sample with a standard level of B Lymphocyte Stimulator or a level of B Lymphocyte Stimulator in cells or a tissue sample from an individual without aberrant B Lymphocyte Stimulator expression, wherein an increase or decrease in the assayed level of B Lymphocyte Stimulator or level in cells or a tissue sample from an individual without aberrant B Lymphocyte Stimulator expression compared to the standard level of B Lymphocyte Stimulator is indicative of aberrant expression.

In specific embodiments, the present invention provides a method for diagnosing a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or activity, comprising:

administering to a subject an effective amount of a labeled antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator;

waiting for a time interval following the administering for permitting the labeled antibody or fragment thereof to preferentially concentrate at sites in the subject where B Lymphocyte Stimulator is expressed;

determining background level; and

detecting the labeled antibody or fragment thereof in the subject, such that detection of labeled antibody or fragment thereof above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of B Lymphocyte Stimulator.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic

agent is horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$ ,  $^{90}\text{Y}$  or  $^{99}\text{Tc}$ .

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is luciferase, luciferin or aequorin.

A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and a pharmaceutically acceptable carrier.

A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and a pharmaceutically acceptable carrier.

A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier.

A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and a pharmaceutically acceptable carrier.

A method of treating, preventing or ameliorating a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

A method of treating, preventing or ameliorating a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid

sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

A method of treating, preventing or ameliorating a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

A method of treating, preventing or ameliorating a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition of comprising at least one antibody or fragment thereof of comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

## EXAMPLES

### Abbreviations

0.2 M Tris-HCl, 0.5 mM EDTA, 0.5 M sucrose (TES)

1-ethyl-3-(3-dimethylaminopropyl)carbo diimide hydrochloride (EDC)

2TY supplemented with 100 µg/ml ampicillin and 2% glucose (2TYAG)

2TY supplemented with 100 µg/ml ampicillin and 50 µg/ml kanamycin (2TYAK)

3,3',5,5'-Tetramethyl Benzidine (TMB)

50% inhibitory concentration ( $\text{IC}_{50}$ )

6xPBS containing 18% Marvel blocking solution (6xMPBS)

Absorbance (A)

Bovine serum albumin (BSA)

Enzyme linked immunosorbent assay (ELISA)

Foetal calf serum (FCS)

Heavy chain variable ( $V_H$ )



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Hepes buffered saline (HBS)  
 Horseradish peroxidase (HRP)  
 Immobilised Metal Affinity Chromatography (IMAC)  
 Isopropyl  $\beta$ -D-thiogalactopyranoside (IPTG)  
 Light chain variable ( $V_L$ )  
 Multiplicity of infection (MOI)  
 N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid] 10  
 (Hepes)  
 Nanomolar (nM)  
 N-Hydroxysuccinimide (NHS)  
 PBS containing 3% Marvel (MPBS)  
 Phosphate Buffered Saline (PBS)  
 Phosphate Buffered Saline+0.1% (v/v) Tween 20 (PBST)  
 Picomolar (pM)  
 Single chain fragment variable (scFv)  
 Tumour Necrosis Factor-alpha (TNF- $\alpha$ )  
 Tumour Necrosis Factor-beta (TNF- $\beta$ )  
 TNF-related apoptosis inducing ligand (TRAIL)

## Definitions:

In the following section "immobilized B Lymphocyte Stimulator" refers to a soluble form of B Lymphocyte Stimulator or biotinylated B Lymphocyte Stimulator coated on a plastic assay plate (e.g., a 96 well plate), but does not refer to histidine tagged B Lymphocyte Stimulator coated on a plastic assay plate; "biotinylated B Lymphocyte Stimulator" is a soluble form of B Lymphocyte Stimulator except when used to coat an ELISA plate, in which case it would be "immobilized B Lymphocyte Stimulator." Membrane bound forms of B Lymphocyte Stimulator include, but are not limited to, U937 and P388 plasma membranes.

## Example 1

## Antibodies Immunospecifically Binding to Soluble and Membrane-Bound B Lymphocyte Stimulator

A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator. Phage displaying scFvs that bound to immobilized B Lymphocyte Stimulator were identified after panning on immobilized B Lymphocyte Stimulator and assessment by ELISA for binding to immobilized B Lymphocyte Stimulator. The B Lymphocyte Stimulator that was immobilized on plates for these assays was purified from supernatants of SP9 cells infected with a baculovirus expression construct as described in Moore et al., Science 285:260-263 which is hereby incorporated by reference in its entirety. Each of the identified scFvs were then sequenced. Certain sequences were isolated multiple times, thus a panel (panel 1) containing one member of each unique sequences was generated and further characterized for their ability to immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator.

The derived amino acid sequences of these scFvs are shown in Table 1 above. The individual  $V_H$  and  $V_L$  segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, which can accessed

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on the United Kingdom Medical Research Council (MRC) Centre for Protein Engineering website) and the closest germline identified.

## Example 2

## Specificity of scFvs for B Lymphocyte Stimulator and Membrane-Bound B Lymphocyte Stimulator

The specificity of each of the scFvs for both B Lymphocyte Stimulator and membrane-bound B Lymphocyte Stimulator was determined by phage ELISA. B Lymphocyte Stimulator was immobilized onto plastic as a purified soluble form of the protein or as a membrane-bound form present on plasma membrane preparations from the human macrophage-like cell line, U937.

## Maintenance of U937 Cells

U937 cells are a human monocyte-like, histiocytic lymphoma cell line known to express B Lymphocyte Stimulator on their plasma membranes. They were maintained in RPMI-1640 supplemented with 4 mM L-glutamine, 10% FCS, 10 U penicillin, 100 g/ml streptomycin (all reagents from Sigma). The cells were thawed from frozen stock and are either used for plasma membrane preparation, or split 1:5, after 2 days in culture when the cell density reaches  $1 \times 10^6$ /ml.

## Preparation of U937 Plasma Membranes

To prepare plasma membranes,  $1 \times 10^9$  U937 cells were harvested from their culture medium by centrifugation at 1000 rpm at 4° C. for 5 minutes in a benchtop centrifuge. The cells were resuspended in 40 ml 12 mM Tris, pH 7.5, 250 mM sucrose and placed on ice. The cells are then lysed using a hand-held electric homogenizer (Labortechnik IKA Ultra-Turrax) for four, one minute, bursts. To check that cell lysis had occurred, 10  $\mu$ l cell lysate was added to 10  $\mu$ l Trypan blue and the cell lysate was examined under a microscope. After confirming lysis, the homogenate was centrifuged at 270xg, for 10 minutes at 4° C. to pellet the nuclear fraction and the supernatant was retained. The supernatant was centrifuged at 8000xg, 10 mins, 4° C., to pellet the mitochondrial and lysosomal fractions and the supernatant was retained. The supernatant was then centrifuged at 100000xg, 60 mins, 4° C. to pellet the plasma membrane enriched fraction. The supernatant was discarded and the plasma membrane pellet was resuspended in 1 ml PBS and stored at -70° C. The protein concentration of the plasma membrane fraction was determined using a protein quantification kit (Biorad). Typical yields were between 5 and 10 mg of plasma membranes.

## Phage ELISA

To determine the specificity of each of the unique scFvs, a phage ELISA was performed for each scFv against human B Lymphocyte Stimulator, U937 plasma membranes, TNF $\alpha$  (R&D Systems, Minneapolis, Minn.), BSA and uncoated well. Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from panel 1 were inoculated into 96-well plates containing 100  $\mu$ l 2TYAG medium per well. Plates were incubated at 37° C. for 4 hours, shaking. M13KO7 helper phage was added to each well to a MOI of 10 and the plates were incubated for a further 1 hour at 37° C. The plates were centrifuged in a benchtop centrifuge at 2000 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 100  $\mu$ l 2TYAK and incubated at 30° C. overnight, shaking. The next day, plates were centrifuged at 2000 rpm for 10 min and

the 100  $\mu$ l phage-containing supernatant from each well carefully transferred into a fresh 96-well plate. Twenty  $\mu$ l of 6xMPBS was added to each well, and incubated at room temperature for 1 hour to pre-block the phage prior to ELISA.

Flexible 96-well plates (Falcon) were coated overnight at 4° C. with human B Lymphocyte Stimulator (1  $\mu$ g/ml) in PBS, U937 plasma membranes (10  $\mu$ g/ml) in PBS, TNF $\alpha$  (1  $\mu$ g/ml) in PBS, BSA (1  $\mu$ g/ml) in PBS, or PBS. After coating, the solutions were removed from the wells, and the plates were blocked for 1 hour at room temperature in MPBS. The plates were washed 3 times with PBS and then 50  $\mu$ l of pre-blocked phage was added to each well. The plates were incubated at room temperature for 1 hour and then washed with 3 changes of PBST followed by 3 changes of PBS. To each well, 50  $\mu$ l of an anti-gene VII- $\alpha$ -HRP conjugate (Pharmacia) at a 1 to 5000 dilution in MPBS was added and the plates incubated at room temperature for 1 hour. Each plate was washed three times with PBST followed by three times with PBS. Then 50  $\mu$ l of an HRP-labelled anti-mouse polymer (DAKO EnVision) diluted 1/50 in 3% MPBS was added and incubated for 1 hour at room temperature. Each plate was then washed three times with PBST followed by three times with PBS. Fifty  $\mu$ l of TMB substrate was then added to each well, and incubated at room temperature for 30 minutes or until colour development. The reaction was stopped by the addition of 25  $\mu$ l of 0.5 M H<sub>2</sub>SO<sub>4</sub>. The signal generated was measured by reading the absorbance at 450 nm (A<sub>450</sub>) using a microtiter plate reader (Bio-Rad 3550).

The results for 3 clones (1006E07, 1008D05 and 1016F04) are shown in FIG. 1. All 3 scFvs recognize immobilized B Lymphocyte Stimulator and U937 plasma membranes but do not recognize TNF $\alpha$ , BSA or an uncoated well (PBS only). These results indicate that these scFvs specifically recognize immobilized B Lymphocyte Stimulator and membrane-bound B Lymphocyte Stimulator.

### Example 3

#### Inhibition in an In Vitro Receptor Binding Assay by Phage ScFvs

All of the unique phage scFvs in panel 1 were assessed for their ability to inhibit soluble B Lymphocyte Stimulator binding to its cognate receptor on IM9 cells.

#### Biotinylation of B Lymphocyte Stimulator

One hundred  $\mu$ g of either human or mouse B Lymphocyte Stimulator was dialysed overnight at 4° C. against 50 mM sodium bicarbonate (sodium hydrogen carbonate) pH8.5 using a slide-a-lyzer cassette (Pierce). The next day, NHS-biotin (Pierce) was dissolved in DMSO to 13.3 mg/ml. This was then added to the B Lymphocyte Stimulator at a molar ratio of 20:1 biotin:B Lymphocyte Stimulator, mixed and incubated on ice for 2 hours. The biotinylated B Lymphocyte Stimulator was then dialysed back into sterile PBS (Sigma) using a slide-a-lyzer cassette overnight at 4° C. The biological activity of the biotinylated B Lymphocyte Stimulator was confirmed using the receptor binding inhibition assay (see below).

#### Maintenance of IM9 Cells

IM9 cells are a human B lymphocyte cell line. They were maintained in RPMI-1640 supplemented with 4 mM L-glutamine, 10% FCS, 10 U penicillin, 100 g/ml streptomycin (all reagents from Sigma). The cells are thawed from frozen stock and can be used in assays after 5 days in culture when they reach a density of 4–8x10<sup>5</sup>/ml.

#### Receptor Binding Inhibition Assay

Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from panel 1 were inoculated into 96-well plates containing 100  $\mu$ l 2TYAG medium per well. Plates were incubated at 37° C. for 4 hours, shaking. M13KO7 helper phage was added to each well to a MOI of 10 and the plates were incubated for a further 1 hour at 37° C. The plates were centrifuged in a benchtop centrifuge at 2000 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 100  $\mu$ l 2TYAG and incubated at 30° C. overnight, shaking. The next day, plates were centrifuged at 2000 rpm for 10 min and the 100  $\mu$ l phage-containing supernatant from each well carefully transferred into a fresh 96-well plate. Phage were diluted 1 in 2 in MPBS prior to use.

Flat-bottomed 96-well plates (Costar) were coated with 100  $\mu$ l per well of a 1:10 dilution of poly-L-lysine (Sigma) in PBS for 1 hour at room temperature. The plates were then washed twice with water, allowed to air-dry and placed at 4° C. overnight. One hundred  $\mu$ l of IM9 cells (at 10<sup>6</sup>/ml in RPMI-1640 culture medium) were then added to each well. Plates were then centrifuged at 3200 rpm for 5 mins to pellet the cells. The media was carefully aspirated and 200  $\mu$ l of MPBS added to each well. The plates were then allowed to block for 1 hour at room temperature.

To a separate 96-well plate 10  $\mu$ l of biotinylated B Lymphocyte Stimulator (at 162.5 ng/ml) in MPBS was added to each well to give a final concentration of 25 ng/ml. Fifty-five  $\mu$ l of each appropriate phage supernatant was added to each well and the final volume in each well was 65  $\mu$ l. Plates were then incubated at room temperature for 30 minutes.

The IM9 coated plates were washed twice in PBS, tapped dry and immediately 50  $\mu$ l of the phage/biotinylated-B Lymphocyte Stimulator mix was added and incubated at room temperature for 1 hour. Plates were washed three times in PBST and three times in PBS, tapped dry and 50  $\mu$ l of streptavidin-Delfia (Wallac) was added to each well at 1:1000 dilution in the Manufacturer's assay buffer. The plates were then incubated at room temperature for 1 hour and washed six times in Delfia wash solution (Wallac). After tapping the plates dry, 100  $\mu$ l per well of Delfia enhancement solution (Wallac) was added. The plates were gently tapped to encourage micelle formation, incubated at room temperature for 10 minutes, and fluorescence read on a Wallac 1420 workstation at 6520 nm.

Results for 3 phage scFvs (1001C09, 1018D07 and 1016H07) that inhibited the binding of biotinylated B Lymphocyte Stimulator are shown in FIG. 2. Maximal binding of biotinylated B Lymphocyte Stimulator to its receptor (bio-B Lymphocyte Stimulator only), the background signal in the absence of biotinylated B Lymphocyte Stimulator (no bio-B Lymphocyte Stimulator), and results with an irrelevant (i.e., does not recognize B Lymphocyte Stimulator) phage antibody are also shown. All 3 phage scFvs inhibited biotinylated B Lymphocyte Stimulator binding to its receptor on IM9 cells, identifying these scFvs as scFvs that bind the soluble form of B Lymphocyte Stimulator. These scFvs also bind to U937 membranes, thus they also bind the membrane bound form of B Lymphocyte Stimulator.

Forty-eight of the scFvs from panel 1 that demonstrated the greatest inhibition as phage particles in this assay were chosen for further study. These 48 scFvs are listed in Table 3.

TABLE 3

scFvs that Inhibit the Binding of Biotinylated-BLyS to its Receptor				
Antibody	Antibody	Antibody	Antibody	Antibody
1008C02	1029D07	1008C03	1008C12	1028A06
1022E02	1061E07	1007H08	1061H01	1031C03
1018C02	1006D07	1008A11	1006D08	1031F02
1008B01	1017D10	1061D02	1022E03	1031F09
1016F04	1007B03	1008A09	1027A07	1031G11
1014E05	1018C10	1007E11	1016H07	1050A07
10018H08	1001C09	1037E07	1021B05	1050A12
1018H09	1018D07	1037E12	1031G10	1050B11
	1029F11	1016F02	1031G08	1051C04
	1022D01		1031C07	1003F12
			1012A06	

## Example 4

## Specificity of Anti-B Lymphocyte Stimulator Antibodies

The specificity of the 48 scFvs listed in Table 3 for human and murine B Lymphocyte Stimulator was determined using phage ELISA.

## Phage ELISA

To determine the specificity of the 48 scFvs, a phage ELISA was performed against human and mouse B Lymphocyte Stimulator, and a panel of related and unrelated human antigens: Fas ligand, TRAIL, TNF $\alpha$ , TNF $\beta$ , and PBS. The Fas ligand, TRAIL, TNF $\alpha$ , and TNF $\beta$  antigens were obtained from R&D Systems, Minneapolis, Minn. Individual *E. coli* colonies containing phagemid were inoculated into 5 ml 2YTAG and incubated at 37° C. for 4 hours, shaking. M13K07 helper phage (Pharmacia) was added to each tube to a MOI of 10 and incubated for 30 minutes at 37° C. for 1 hour, the first 30 minutes static and the final 30 minutes with gentle shaking. Cells were pelleted by centrifugation at 3,500 rpm for 10 minutes and the supernatant discarded. Cell pellets were resuspended in 5 ml 2TYAK and incubated at 30° C. overnight with shaking. The next day, the cells were pelleted by centrifugation at 3,500 rpm for 10 minutes. The phage-containing supernatant (5 ml) was carefully transferred to a fresh tube, 1 ml of 6MPBS was added, and the tube was incubated at room temperature for 1 hour to pre-block the phage prior to ELISA.

All antigens were coated at 1  $\mu$ g/ml. ELISAs were performed essentially as described in Example 2. The only exception to this being the detection of phage antibody binding to mouse B Lymphocyte Stimulator where the step involving incubation with the HRP-labelled anti-mouse polymer was omitted. Binding to mouse B Lymphocyte Stimulator was detected with TMB as in Section Example 2.

All 48 scFvs are specific for immobilized human B Lymphocyte Stimulator and 43 out of the 48 scFvs cross-react with immobilized mouse B Lymphocyte Stimulator but not with any other unrelated or related antigen tested. 1008C03, 1007F11, 1037E07, 1037E12, and 1016H07 did not bind murine B Lymphocyte Stimulator. Results for two scFvs, 1022D01 and 1031F02, are shown in FIG. 3. Both these scFvs specifically recognize human and mouse B Lymphocyte Stimulator but not any other unrelated or related antigen tested.

## Specificity for the Membrane-Bound Form of B Lymphocyte Stimulator

The specificity of 48 scFvs for membrane-bound B Lymphocyte Stimulator was determined by the phage ELISA described in Example 2. B Lymphocyte Stimulator was immobilized onto plastic as a membrane-bound form present on plasma membranes preparations from the human macrophage-like cell line, U937. This cell line is known to express the membrane-bound form of human B Lymphocyte Stimulator.

To demonstrate that this binding is specific for membrane-bound B Lymphocyte Stimulator, a competition ELISA was developed to determine if the ELISA signal for an individual antibody on U937's could be competed out by pre-incubation with either B Lymphocyte Stimulator or TNF $\alpha$ . An anti-B Lymphocyte Stimulator antibody that also recognizes membrane-bound B Lymphocyte Stimulator would be expected to demonstrate a signal reduction with free B Lymphocyte Stimulator but not free TNF $\alpha$ .

## Competition ELISA

Individual *E. coli* colonies containing phagemid for each of the 48 scFvs listed in Table 3 were inoculated into 5 ml 2YTAG and incubated at 37° C. for 4 hours, shaking. M13K07 helper phage (Pharmacia) was added to each tube to a MOI of 10 and incubated for 30 minutes at 37° C. for 1 hour, the first 30 minutes static and the final 30 minutes with gentle shaking. Cells were pelleted by centrifugation at 3,500 rpm for 10 minutes and the supernatant discarded. Cell pellets were resuspended in 5 ml 2TYAK and incubated at 30° C. overnight with shaking. The next day, the cells were pelleted by centrifugation at 3,500 rpm for 10 minutes. The phage-containing supernatants (5 ml) were carefully transferred to a fresh tube.

For each of the 48 scFvs listed in Table 3, two aliquots of 20  $\mu$ l 6xMPBS were pipetted into separate wells of a 96-well plate (Greiner). The first aliquot was supplemented with B Lymphocyte Stimulator to a final concentration of 0.5  $\mu$ g/ml. The second aliquot was supplemented with TNF $\alpha$  to a final concentration of 0.5  $\mu$ g/ml. Each experiment was performed in triplicate. One hundred  $\mu$ l of each phage supernatant was then added to each aliquot and mixed by pipetting up and down. The phage were incubated ( $\pm$ competing antigen) at room temperature for 1 hour.

Flexible 96-well plates (Falcon) were coated overnight at 4° C. with 50  $\mu$ l of 10  $\mu$ g/ml U937 plasma membranes. After coating, the plates were washed 3 times with PBS and blocked for 1 hour at room temperature with 200  $\mu$ l MPBS. The plates were washed 3 times with PBS and 50  $\mu$ l of phage ( $\pm$ competing antigen) was added to each appropriate well. The plates were incubated at room temperature for 1 hour and then washed with 3 changes of PBST followed by 3 changes of PBS. To each well, 50  $\mu$ l of a mouse anti-gene VIII-HRP conjugate (Pharmacia) at a 1:5000 dilution in MPBS was added and the plates incubated at room temperature for 1 hour. Each plate was washed three times with PBST followed by three times with PBS. Then 50  $\mu$ l of an HRP-labelled anti-mouse polymer (DAKO EnVision) diluted 1:50 in 3% MPBS was added and incubated for 1 hour at room temperature. Each plate was then washed three times with PBST followed by three times with PBS. Fifty  $\mu$ l of TMB substrate was then added to each well, and incubated at room temperature for 30 to 60 minutes or until color development. The reaction was stopped by the addition of 25

$\mu\text{l}$  of 0.5 M  $\text{H}_2\text{SO}_4$ . The signal generated was measured by reading the absorbance at 450 nm ( $A_{450}$ ) using a microtiter plate reader (Bio-Rad 3550).

All 48 scFvs bind to U937 plasma membrane preparations. This signal could be competed out by pre-incubation of the phage antibody with B Lymphocyte Stimulator but not by pre-incubation with TNF- $\alpha$ . This indicates that the 48 scFvs specifically recognize membrane-bound B Lymphocyte Stimulator as well as soluble B Lymphocyte Stimulator. Typical results are exemplified by scFvs 1031F09, 1050A12 and 1051C04 and are shown in FIG. 4. All 3 scFvs demonstrate binding to U937 plasma membranes. This binding was specifically competed out with B Lymphocyte Stimulator but did not compete with TNF- $\alpha$ , demonstrating specific recognition of membrane-bound B Lymphocyte Stimulator.

#### Example 6

##### scFv Off-Rate Determinations

All off-rate determinations were performed on BIAcore 2000 machines, using the BIAcore 2000 Control Software and evaluated using the BIAevaluation 3.0 software.

##### Preparation of a Low Density B Lymphocyte Stimulator Surface

A 500 RU surface was prepared for kinetic studies with purified scFvs. A low density B Lymphocyte Stimulator surface (500 RU B Lymphocyte Stimulator coupled) was prepared in flow cell 2 by amine coupling to a CM5 chip. A new CM5 chip was inserted into the BIAcore and a sensorgram initiated with HBS buffer at a flow rate of 5  $\mu\text{l}/\text{min}$ . The NHS and EDC coupling solutions (BIAcore) were mixed according to manufacturer's instructions and 30  $\mu\text{l}$  injected over the CM5 surface. Fifty  $\mu\text{l}$  of B Lymphocyte Stimulator at 1  $\mu\text{g}/\text{ml}$  in 10 mM sodium acetate buffer, pH4, was then injected followed by 30  $\mu\text{l}$  of ethanolamine-HCl solution (BIAcore). The flow rate was then adjusted to 20  $\mu\text{l}/\text{min}$  and 10  $\mu\text{l}$  of 4M guanidine hydrochloride in HBS injected over the surface. This strips the surface of non-covalently bound B Lymphocyte Stimulator.

##### Measurement of scFv Off-Rate Kinetics on the Low Density Surfaces

The chip containing the low density B Lymphocyte Stimulator surface was inserted in to the BIAcore. A dilution series of purified scFvs was prepared in HBS, typically 50  $\mu\text{g}/\text{ml}$  doubling dilutions down to 1.5  $\mu\text{g}/\text{ml}$ . The dilution series was then injected sequentially over the low density B Lymphocyte Stimulator surface (and blank control) using the following program:

MAIN			
FLOWCELL	1,2,3,4		
APROG	genab	r1d1	ab1
APROG	genab	r1d2	ab2
APROG	genab	r1d3	ab3
APROG	genab	r1d4	ab4
APROG	genab	r1d5	ab5
APROG	genab	r1d6	ab6
END			
APPEND CONTINUE			
DEFINE APROG	genab		
PARAM %Apos	%AbId		
FLOW	20		
KINJECT	%Apos 200 80		

-continued

INJECT	r1c6 10/guanidine hydrochloride regeneration step
EXTRACT/AN	
END	

Bound scFvs were removed by injecting 10  $\mu\text{l}$  4M GuHCl in HBS over the surface between scFv samples.

The binding curves for individual scFvs were analyzed using the BIAevaluation software to determine antibody off-rates. Kinetic analysis for a typical scFv antibody, 1003C02, is shown in FIG. 5. 1003C02 has a  $K_{off}$  of  $6 \times 10^{-3} \text{ s}^{-1}$ .

#### Example 7

##### Inhibition in an In Vitro Receptor Binding Assay by scFv Antibodies

The 48 scFvs listed in Table 3 were purified and assessed for their ability to inhibit B Lymphocyte Stimulator binding to its receptor on IM9 cells.

##### 25 Purification of scFv

To determine the inhibitory potency of anti-B Lymphocyte Stimulator scFv, scFv's were first prepared by IMAC. 2TYAG (5 ml) was inoculated with a single colony and grown overnight at 30° C., shaking. This overnight culture was then used to inoculate 500 ml of 2TY containing 100  $\mu\text{g}/\text{ml}$  ampicillin and 0.1% Glucose, and grown at 30° C., shaking, until an  $A_{600}$  of 1.0 was attained. IPTG was added to 1 mM and the culture was grown for a further 3.5 hours at 30° C.

Cells were harvested by centrifugation at 5,000 rpm, and resuspended in 10 ml of TES. A further 15 ml of a 1:5 dilution (in water) of TES was added, and the cell suspension incubated on a turning wheel at 4° C. for 30 minutes. This causes osmotic shock and yields a periplasmic extract containing the scFv. Residual cells and debris were pelleted by centrifugation at 9,000 rpm for 20 minutes at 4° C. The supernatant was transferred to a new tube, and 50  $\mu\text{l}$  of 1 M  $\text{MgCl}_2$  added. Two ml of a Ni-NTA agarose (Qiagen), pre-washed with buffer (50 mM sodium phosphate, pH 8, 300 mM NaCl) together with a protease inhibitor tablet (Boehringer Mannheim) were then added to the periplasmic extract. The preparation was incubated, rotating, overnight at 4° C. The Ni-NTA was pelleted by centrifugation at 2,000 rpm for 5 minutes, and the supernatant was aspirated. The agarose beads were washed 3 times with 50 ml wash buffer, centrifuging to collect the agarose in between each wash. Ten ml of wash buffer was added after the final wash, and the slurry was loaded on to a polyrep column (BioRad). Two ml elution buffer (50 mM NaPi (sodium phosphate), pH 8, 300 mM NaCl, 250 mM imidazole) was added to the drained agarose, and the eluate was collected. IMAC purified scFv was buffer exchanged in to PBS by use of a Nap 5 column (Pharmacia) according to the manufacturer's instructions. The  $A_{280}$  was read and the protein concentration determined using a molar extinction coefficient of 1 mg/ml protein  $\times A_{280}$  1.4. Purified scFv was stored in 500  $\mu\text{l}$  aliquots at -70° C.

##### Receptor Binding Inhibition Assay

Flat-bottomed 96-well plates (Costar) were coated with 100  $\mu\text{l}$  per well of a 1:10 dilution of poly-L-lysine (Sigma) in PBS for 1 hour at room temperature. The plates were then washed twice with water, allowed to air-dry and placed at 4°

C. overnight. One hundred  $\mu$ l of IM9 cells (at  $10^6$ /ml in RPMI-1640) were then added to each well. Plates were then centrifuged at 3200 rpm for 5 mins to pellet the cells. The media was carefully aspirated and 200  $\mu$ l of MPBS added to each well. The plates were then left to block for 1 hour at room temperature.

To a separate 96-well plate, titrate test scFvs in MPBS, in triplicate, over a concentration range from 10  $\mu$ g/ml down to 0.001  $\mu$ g/ml were added. The final volume of test scFv in each well was 55  $\mu$ l. Competition with unlabelled B Lymphocyte Stimulator was also included in every assay as a control. Unlabelled B Lymphocyte Stimulator, in MPBS, was typically titrated in triplicate, over a concentration range from 1  $\mu$ g/ml down to 0.001  $\mu$ g/ml. 10  $\mu$ l of biotinylated-B Lymphocyte Stimulator (at 162.5 ng/ml) in MPBS was added to each well to give a final concentration of 25 ng/ml. Plates were then incubated at room temperature for 30 minutes.

The IM9 coated plates was washed twice in PBS, tapped dry and immediately 50  $\mu$ l of the scFv/biotinylated-B Lymphocyte Stimulator mix was added and incubated at room temperature for 1 hour. Plates were washed three times in PBST and three times in PBS, tapped dry and 50  $\mu$ l per well added of streptavidin-Delfia (Wallac) at 1:1000 dilution in the Manufacturer's assay buffer. The plates were then incubated at room temperature for 1 hour and washed six times in Delfia wash solution (Wallac). After tapping the plates dry, 100  $\mu$ l per well of Delfia enhancement solution (Wallac) was added. The plates were gently tapped to encourage micelle formation, incubated at room temperature for 10 minutes, and fluorescence read on a Wallac 1420 workstation at 6520 nm.

Typical titration curves for two scFv antibodies, 1007F11 and 1050A07, are shown in FIG. 6. Unlabelled B Lymphocyte Stimulator competed for binding to its receptor with an  $IC_{50}$  value of 0.8 nM. The  $IC_{50}$  values for 1007F11 and 1050A07 are 7.9 nM and 17.1 nM, respectively. The assay was performed in triplicate and standard error bars are shown. The 9 scFvs that demonstrated the greatest inhibition as scFv are listed in Table 4. This data also confirms that these 9 scFvs recognize the soluble form of B Lymphocyte Stimulator.

TABLE 4

ScFvs that demonstrated greatest potency in BlyS Receptor Binding Inhibition Assay	
ScFv Antibody	
1017D10	
1022D01	
1008A11	
1006D08	
1031F02	
1050A12	
1050B11	
1051C04	
1003F12S	

Example 8

#### Antibodies Recognizing a Soluble Form of B Lymphocyte Stimulator

A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the soluble but not the membrane-bound forms of B Lymphocyte Stimulator.

A phage library was screened for the ability to bind to biotinylated B Lymphocyte Stimulator. The phage were exposed to biotinylated B Lymphocyte Stimulator, allowed an interval of time to bind the biotinylated B Lymphocyte Stimulator. Phage binding bio-B Lymphocyte Stimulator were then isolated by capture on streptavidin coated magnetic beads.

The phage identified in the screen above (capture of Bio-B Lymphocyte Stimulator from solution) were then screened by ELISA for their ability to bind immobilized B Lymphocyte Stimulator. The scFv expressed by phage that bound immobilized B Lymphocyte Stimulator were then cloned and sequenced. Again, several sequences were identified multiple times, thus a panel (panel 2) consisting of an example of each phage expressing a unique scFv was then characterized further.

The derived amino acid sequences of these scFvs are shown in Table 1 above. The individual  $V_H$  and  $V_L$  segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, which can accessed on the United Kingdom Medical Research Council (MRC) Centre for Protein Engineering website) and the closest germline identified.

#### Example 9

##### Specificity For Soluble B Lymphocyte Stimulator

The scFvs were isolated from a library of phage based on their ability to bind a soluble form of B Lymphocyte Stimulator. Briefly, phage were preincubated with biotinylated B Lymphocyte Stimulator in solution. Phage that bound to this biotinylated B Lymphocyte Stimulator were then isolated using streptavidin coated magnetic beads.

The specificity of each of the unique scFvs for B Lymphocyte Stimulator and for the membrane-bound form of B Lymphocyte Stimulator, was determined by phage ELISA. B Lymphocyte Stimulator was immobilised onto plastic as a purified soluble form of the protein or as a membrane-bound form present on plasma membrane preparations from the human macrophage-like cell line, U937. Maintenance of U937 cells and plasma membrane preparations were performed as detailed in Example 2.

##### Phage ELISA

To determine the specificity of each of the scFvs, a phage ELISA was performed for each antibody against human B Lymphocyte Stimulator, U937 plasma membranes, TNF $\alpha$ , BSA and an uncoated well. Antigen coating conditions were as described in Example 2, apart from human B Lymphocyte Stimulator. B Lymphocyte Stimulator was first biotinylated (as described in Example 3) and coated at 1  $\mu$ g/ml onto streptavidin coated plates (Reacti-Bind, Pierce) for 30 mins at room temperature. The plates were then washed, blocked and the phage ELISA performed as detailed in Example 2.

The results for 3 clones (1074B12, 1075F12 and 1075A02) that bind the soluble but not the membrane-bound form of B Lymphocyte Stimulator are shown in FIG. 7. As a control, a phage antibody that recognizes TNF $\alpha$ , is also shown in FIG. 7. There is a small non-specific background signal on the U937 plasma membranes that is evident with both the anti-B Lymphocyte Stimulator scFvs as well as the anti-TNF $\alpha$  control. All 3 anti-B Lymphocyte Stimulator scFvs recognize B Lymphocyte Stimulator but not U937 plasma membranes, TNF $\alpha$ , BSA or an uncoated well (PBS only). This indicates that the scFvs do not bind the membrane-bound form of B Lymphocyte Stimulator. Further, The fact

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that these scFvs were isolated on the basis of their ability to bind soluble biotinylated B Lymphocyte Stimulator indicates that they bind the soluble form of B Lymphocyte Stimulator. Further confirmation of these scFvs' specificity for B Lymphocyte Stimulator is provided in Example 10.

## Example 10

## Inhibition in an In Vitro Receptor Binding Assay by Phage scFvs

All of the unique phage scFvs from panel 2 were assessed for their ability to inhibit B Lymphocyte Stimulator binding to its cognate receptor on IM9 cells. The biotinylation of B Lymphocyte Stimulator, maintenance of IM9 cells and receptor binding inhibition assay were performed as described in Example 3.

Results for two phage scFvs, 10025B09 and 1026C04 are shown in FIG. 8. Maximal binding of biotinylated B Lymphocyte Stimulator to its receptor (bio-B Lymphocyte Stimulator only), the background signal in the absence of biotinylated B Lymphocyte Stimulator (no bio-B Lymphocyte Stimulator), and results with an irrelevant (i.e. does not recognize B Lymphocyte Stimulator) phage antibody are also shown. Both phage scFvs inhibited biotinylated B Lymphocyte Stimulator binding to its receptor on IM9 cells. 33 of the unique scFvs from panel 2 were identified for further study. These 33 scFvs demonstrated the greatest inhibition as phage particles in this assay and are listed in Table 5.

TABLE 5

Identification of 33 phage scFvs to free BlyS that demonstrates the most significant inhibition of biotinylated-BlyS binding to its receptor

Antibody	Antibody	Antibody	Antibody
1026C04	1074B12	1073F04	1065D04
1003C06	1075A02	1078D08	1068C08
1025B09	1068B08	1078D02	1068F03
1027B12	1068B04	1075G01	1069B07
1025B06	1068C06	1071B03	
1030A10	1075F12	1072B09	
1002A01R	1065D08	1078B08	
1002A01K	1065F08	1064C04	
1026C04R	1067B10	1064C07	
1026C04K	1067F05		

## Example 11

## Specificity of Anti-B Lymphocyte Stimulator scFvs

The specificity of the 33 scFvs (listed in Table 5) for immobilized human and murine B Lymphocyte Stimulator was determined using phage ELISA.

## Phage ELISA

To determine the specificity of the 33 scFvs, a phage ELISA was performed as described in Example 4 against human and mouse B Lymphocyte Stimulator, and a panel of related human antigens: TRAIL, LIGHT, TNF $\alpha$ , TNF $\beta$ , and an uncoated well (PBS only).

Typical results for two scFvs, 1067F05 and 1078D02 are shown in FIG. 9. A control antibody that specifically recognizes TNF $\alpha$  is also shown. Both anti-B Lymphocyte Stimulator scFvs specifically recognize immobilized human and mouse B Lymphocyte Stimulator but not any other antigen tested.

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All 33 scFvs are specific for human B Lymphocyte Stimulator. 14/33 cross-react with mouse B Lymphocyte Stimulator but not with any other unrelated or related antigen tested.

## Example 12

## scFv Off-Rate Determinations

Off-rate determinations, preparation of a low density B Lymphocyte Stimulator surface and kinetic measurements were as detailed in Example 6.

The binding curves for individual scFvs were analysed using the BIAevaluation software to determine antibody off-rates. Kinetic analysis for a typical scFv antibody, 1002A01, is shown in FIG. 10. 1002A01 has a  $K_{off} = 9 \times 10^{-4} \text{ s}^{-1}$ .

## Example 13

## Inhibition in an In Vitro Receptor Binding Assay by scFv Antibodies

The 33 scFvs identified in Table 5 were prepared as purified scFvs and assessed for their ability to inhibit B Lymphocyte Stimulator binding to its receptor on IM9 cells. The scFvs were purified and analysed in the receptor binding inhibition assay as described in Example 6.1.8.

Typical titration curves for two scFvs, 10068C06 and 1074B12, are shown in FIG. 11. Unlabelled B Lymphocyte Stimulator competed for binding to its receptor with an inhibitory constant 50 ( $IC_{50}$ ) value of 0.66 nM. The  $IC_{50}$  values for 10068C06 and 1074B12 are 61 nM and 13 nM, respectively. The assay was performed in triplicate and standard error bars are shown. The 7 scFvs that demonstrated the greatest inhibition as scFv are listed in Table 6.

TABLE 6

Identification of 7 scFvs to free BlyS that demonstrate the most significant inhibition of biotinylated-BlyS binding to its receptor as purified scFvs.

Antibody
1002A01-R
1002A01-K
1026C04-R
1026C04-K
1068C06
1075F12
1067B10

## Example 14

## ScFvs Recognizing Membrane-Bound B Lymphocyte Stimulator

A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the membrane-bound but not the soluble form of B Lymphocyte Stimulator.

As a starting point, a library of phage expressing scFv antibodies were panned on immobilized HIS-tagged B Lymphocyte Stimulator. Phage isolated by panning were then screened for the ability to bind to HIS-tagged B Lymphocyte Stimulator. HIS-tagged B Lymphocyte Stimulator was obtained by expressing amino acids 71-285 of SEQ ID

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NO:3228 using the pQE9 vector (Qiagen Inc., Valencia, Calif.) in *E. coli* and purifying the expressed protein. This phage clones identified by this screen were then sequenced. After sequencing, A panel (panel 3) of phage each expressing a unique scFv that bound His-tagged B Lymphocyte Stimulator was generated and further characterized.

The derived amino acid sequences of the unique scFvs from panel 3 are shown in Table 1 above. The individual  $V_H$  and  $V_L$  segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, which can accessed on the United Kingdom Medical Research Council (MRC) Centre for Protein Engineering website) and the closest germline identified.

## Example 15

## Recognition of Membrane-Bound B Lymphocyte Stimulator

The specificity of each of the unique scFvs for both the membrane-bound form of B Lymphocyte Stimulator as well as for the soluble form of B Lymphocyte Stimulator, was determined by phage ELISA.

B Lymphocyte Stimulator was immobilised onto plastic either directly as a purified soluble form of the protein or biotinylated and coated on a streptavidin plate as in Example 9. Binding to His-tagged B Lymphocyte Stimulator was used as a primary screen for scFv's that would bind the membrane-bound form of B Lymphocyte Stimulator (see below). The membrane-bound form of B Lymphocyte Stimulator was presented as plasma membranes preparations from the human macrophage-like cell line, U937 or the murine cell line P388.

Mouse monoclonal antibodies have been raised against His-tagged B Lymphocyte Stimulator according to standard procedures. Characterization of these mouse monoclonal antibodies revealed that they specifically recognized both His-tagged B Lymphocyte Stimulator and the membrane-bound form of B Lymphocyte Stimulator on U937 cells, but not soluble B Lymphocyte Stimulator. Therefore, specific recognition of His-tagged B Lymphocyte Stimulator was used as supporting evidence for the recognition of the membrane-bound form of B Lymphocyte Stimulator by phage and scFv antibodies.

## Phage ELISA

To determine the specificity of each of the scFvs, a phage ELISA was performed for each antibody against His-tagged human B Lymphocyte Stimulator, U937 plasma membranes, TNF $\alpha$ , BSA and an uncoated well. Antigen coating conditions were as described in 2. apart from human B Lymphocyte Stimulator. B Lymphocyte Stimulator was first biotinylated (as described in Example 3) and coated at 1  $\mu$ g/ml onto streptavidin coated plates (Reacti-Bind, Pierce) for 30 mins at room temperature. The plates were then washed, blocked and the phage ELISA performed as detailed in Example 2.

The results for 3 clones, 1079C01, 1081C10 and 1082A02, and a control phage antibody that recognizes TNF $\alpha$ , are shown in FIG. 12. All 3 scFvs recognize U937 plasma membranes (U937) and His-tagged B Lymphocyte Stimulator (His-B Lymphocyte Stimulator) but not, biotinylated B Lymphocyte Stimulator (bio-B Lymphocyte Stimulator) or an uncoated well (PBS). This indicates that the scFvs recognize the membrane-bound form of B Lymphocyte Stimulator.

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## Example 16

## Specificity for Membrane-Bound B Lymphocyte Stimulator

The specificity of the scFvs for only the membrane-bound form of B Lymphocyte Stimulator, and not for the soluble form, was confirmed using a competition ELISA. This assay assesses the ability of test phage scFvs to bind to the membrane-bound form of B Lymphocyte Stimulator on U937 plasma membranes in the presence of different forms of competing B Lymphocyte Stimulator. Competing B Lymphocyte Stimulator was either the His-tagged form of B Lymphocyte Stimulator or soluble B Lymphocyte Stimulator. ScFvs specific for the membrane-bound B Lymphocyte Stimulator would be expected to be competed out by pre-incubation with His-tagged B Lymphocyte Stimulator but not by pre-incubation with soluble B Lymphocyte Stimulator.

Maintenance of U937 cells and plasma membrane preparations were performed as detailed in Example 2.

## Competition ELISA

U937 plasma membranes (50  $\mu$ l per well) were coated at 10  $\mu$ g/ml in PBS onto Falcon 96-well plates overnight at 4° C.

Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from the panel 3 were inoculated into 50 ml tubes (Falcon) containing 5 ml 2TYAG medium. Tubes were incubated at 37° C. for 4 hours, shaking. M13KO7 helper phage was added to each tube to an MOI of 10 and the tubes were incubated for a further 1 hour at 37° C. The tubes were centrifuged in a benchtop centrifuge at 3500 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 5 ml 2TYAK and incubated at 30° C. overnight, shaking. The next day, tubes were centrifuged at 3500 rpm for 10 min and the phage-containing supernatant carefully transferred into a fresh tube.

For each test phage antibody, 3 aliquots of 20  $\mu$ l 18% marvel/6xPBS were transferred into separate wells of a 96-well plate. The first aliquot was supplemented with His-tagged B Lymphocyte Stimulator to a final concentration of 60  $\mu$ g/ml. The second aliquot was supplemented with soluble B Lymphocyte Stimulator to a final concentration of 60  $\mu$ g/ml. The third aliquot was not supplemented with any competing antigen. One hundred  $\mu$ l of phage supernatant was then added to each aliquot and left to block at room temperature for 1 hour.

The antigen-coated plates were washed once with PBS before the addition of 200  $\mu$ l/well 3% marvel/PBS. These plates were left to block at 37° C. for 1 hour and were then washed once with PBS. Duplicate samples of 50  $\mu$ l pre-blocked phage (above) were added to the antigen-coated plates and left at room temperature for 1 hour. Plates were washed 3x with PBS/0.1% Tween 20, then 3x with PBS. Fifty  $\mu$ l/well mouse anti-M13 HRP (Pharmacia) at  $\frac{1}{500}$  in 3% Marvel/PBS was added and left for 1 hour at room temperature. Plates were washed 3 times with PBS/0.1% Tween 20, then 3 times with PBS. Fifty  $\mu$ l/well HRP-labelled anti-mouse Envisio polymer (DAKO) at 1/50 in 3% marvel/PBS was added and left for 1 hour at RT. Plates were washed 3 times with PBS/0.1% Tween 20, then 3 times with PBS. Next, 50  $\mu$ l/well of TMB (Sigma) was added and plates left to develop for 30 to 60 minutes. When sufficient color has developed, 25  $\mu$ l/well 0.5M H<sub>2</sub>SO<sub>4</sub> was added to

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stop the reaction. The plates were read at 450 nm on a microtiter plate reader (Bio-Rad 3550).

The results for 3 clones, 1079B04, 1079F08 and 1080B01, and a control phage antibody that recognizes TNF $\alpha$ , are shown in FIG. 13. All 3 scFvs recognize U937 plasma membranes (U937). This binding is competed out to background levels (i.e. comparable to the signal observed with the anti-TNF $\alpha$  phage antibody) in the presence of His-tagged B Lymphocyte Stimulator (HIS-B Lymphocyte Stimulator) but not biotinylated B Lymphocyte Stimulator (bio-B Lymphocyte Stimulator). This confirms that the scFvs specifically recognize the membrane-bound form but not the soluble form of B Lymphocyte Stimulator.

## Example 17

## High Throughput BIAcore Screen to Identify High Affinity scFvs

This is a 96-well screen where the test samples (scFvs) are derived from 1 ml periplasmic extracts of individual antibody expressing clones. Potentially higher affinity scFvs are then identified principally as those giving a large number of total RU's bound to a HIS-B Lymphocyte Stimulator surface in BIAcore. This method of ranking does assume approximately equal yields of scFv from each clone. Since this is not always the case, some scFvs may also be identified that simply express high levels of scFv. These can be discriminated from those of higher affinity by further characterization of the scFvs (see Example 18).

Preparation of ScFv from 1 ml *E. coli* Cultures

Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from panel 3 were inoculated into 96-well plates containing 100  $\mu$ l 2TYAG medium per well. Eight wells on each plate were reserved for positive and negative control samples. The plate was grown overnight at 30° C. with shaking at 120 rpm.

Next day, 1 ml of 2TYAG+345 mM sucrose was added to each well of an autoclaved 96 deep well plate (Beckman). Twenty  $\mu$ l of each overnight culture was resuspended and transferred to the appropriate well of the deep well plate. The plate was grown for approximately 3.5 hours at 30° C. with shaking at 250 rpm (or until the OD<sub>600</sub>~0.6). Fifty  $\mu$ l of 1M IPTG was added to 5 ml 2TY and 10  $\mu$ l of this was added to each well. The plate was grown overnight at 30° C. with shaking at 250 rpm.

Plates were kept at 4° C. for the remainder of the procedure. The overnight plate (above) was centrifuged at 3500 rpm for 10 minutes at 4° C. to pellet the cells. The supernatant was decanted and each pellet resuspended in 100  $\mu$ l TES (0.2M Tris HCl pH8.0, 0.5 mM EDTA, 0.5M sucrose) and transferred to a fresh 96 well plate. This plate was incubated on ice for 30 minutes and then centrifuged for 10 minutes at 3500 rpm at 4° C. to pellet the cell debris. During centrifugation, 15  $\mu$ l of freshly made protease inhibitors cocktail (Roche, 1 tablet dissolved in 1.5 ml water) was added to each well of a fresh 96 well plate. Supernatants from the centrifuged plate were then transferred to the plate containing the protease inhibitors. The plate was centrifuged at 3500 rpm for 10 minutes at 4° C. and the supernatant was transferred to a further 96-well plate. This step was repeated at least once more or until there was no sign of any cell debris following centrifugation. Finally, the plate was covered in foil to prevent evaporation of samples during the BIAcore run.

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## Generation of a High Density HIS-B Lymphocyte Stimulator Surface

All BIAcore analysis was performed on BIAcore 2000 machines, using the BIAcore 2000 control software and evaluated using the BIAevaluation 3.0 software. A high density His-tagged B Lymphocyte Stimulator surface (>1000 RU HIS-B Lymphocyte Stimulator coupled) was prepared in flow cell 2 by amine coupling to a CM5 chip. A new CM5 chip was inserted into the BIAcore and a sensorgram started over flow cell 2 with HBS buffer at a flow rate of 5  $\mu$ l/min. The NHS and EDC solution were mixed 1:1 before injecting 30  $\mu$ l over the CM5 surface. Fifty  $\mu$ l HIS-B Lymphocyte Stimulator (at 10  $\mu$ g/ml in Sodium acetate buffer, pH4) was injected and allowed to couple to the surface. Thirty  $\mu$ l of ethanolamine-HCl solution was then injected to block free NHS esters. Prior to using the chip, 10  $\mu$ l of 4M Guanidine hydrochloride in HBS was injected over the surface to strip the surface of non-covalently bound B Lymphocyte Stimulator. A blank surface (no HIS-B Lymphocyte Stimulator) was also prepared over flow cell 1 so that non-specific binding effects can be subtracted from the HIS-B Lymphocyte Stimulator binding curves.

Typically, a 5000 RU His-tagged B Lymphocyte Stimulator surface was generated in this way and used for 96-well analysis of scFvs isolated from the periplasm of *E. coli*.

## BIAcore Analysis

The 96-well plate containing periplasmic scFvs was secured inside the BIAcore. Two ml of 4M Guanidine hydrochloride in HBS was placed in a rack inside the BIAcore for regeneration of the HIS-B Lymphocyte Stimulator surface between samples. The sensorgram was run over flow cells 1 and 2 at a flow rate of 20  $\mu$ l/minute. The following method was run:

## MAIN

FLOWCELL 1,2,3,4

LOOP cycle STEP

APROG inj % pos

ENDLOOP

APPEND CONTINUE

END

DEFINE LOOP cycle

LPARAM % pos

r1a1

r1b1

r1c1

r1d1

r1e1

r1f1 etc (all wells listed until r1h12)

END

DEFINE APROG inj

PARAM % pos

FLOW 20

KINJECT % pos 35 30 %scfv injection



QUICKINJECT r2f3 10<sup>6</sup> regeneration  
EXTRACLEAN

END

When the run had finished, the sensorgram data for flow cell 1 was subtracted from the data for flow cell 2 for each sample using the BIAevaluation software. The clones were compared with one another principally by overall RU change as the scFv dissociates from the surface. In addition a few scFvs were identified as having potentially slower off-rates. An example of the dissociation section of a typical sensorgram for 8 scFvs is shown in FIG. 14. An anti-TNF $\alpha$  antibody that does not recognize B Lymphocyte Stimulator was included as a control. Of the 8 scFvs exemplified, 1079F06 was identified for further study due to the relatively high numbers of RU's bound to the surface.

ScFvs were identified principally if they demonstrated a RU change of over 1200, a few were also identified as having potentially slower than typical off-rates. A total of 28 clones were chosen on these criteria and are listed in Table 7.

TABLE 7

Identification of 28 antibodies to membrane-bound BLyS that demonstrate the most significant RU changes by BIAcore	
Antibody	Antibody
1079C01	1084C04
1082H08	1080E05
1079E02	1083B12
1079B05	1082G01
1079F06	1082G02
1079F06	1082C03
1079F11	1082A05
1079B12	1082D07
1080B01	1082B08
1080G09	1084A01
1099D03	1084B02
1080D03	1080A08
1080A03	1084C11
1083G03	
1080G07	

## Example 18

## scFv Affinity Determinations

The affinity ( $K_D$ ) of the 28 scFvs was determined using the BIAcore.

## Low Density HIS-B Lymphocyte Stimulator Surface for Kinetic Studies

500 RU surfaces were used for kinetic studies of purified scFv binding to HIS-B Lymphocyte Stimulator. The method to prepare these surfaces was identical to the method described in Example 17, only smaller volumes of HIS-B Lymphocyte Stimulator were injected.

## Measurement of scFv Binding Kinetics

The chip containing the low density HIS-B Lymphocyte Stimulator surface was inserted into the BIAcore. A dilution series for each of the 28 purified scFvs (prepared as in Example 6) were diluted in HBS (typically starting with 50  $\mu$ g/ml scFv and double diluting down to 1.5  $\mu$ g/ml). The dilution series was then injected sequentially over the blank control (flow cell 1) and low density HIS-B Lymphocyte Stimulator surface (flow cell 2) using the following program:

```

MAIN
FLOWCELL 1,2,3,4
APROG          genab      r1d1      ab1
APROG          genab      r1d2      ab2
APROG          genab      r1d3      ab3
APROG          genab      r1d4      ab4
APROG          genab      r1d5      ab5
APROG          genab      r1d6      ab6
APPEND CONTINUE
END
DEFINE APROG genab
PARAM %Apos %AbId
FLOW          20
KINJECT       %Apos 200 80
INJECT        r2f3 10
EXTRACLEAN
END

```

Bound scFv were removed by injecting 10  $\mu$ l of 4M Guanidine hydrochloride in HBS (location r2f3 in the above program) over the surface between samples. Binding curves for individual scFv were analysed using the BIAevaluation software to determine antibody on- and off-rates.

A typical example of the binding curves generated for the scFv antibody 1082C03 is shown in FIG. 15. The off-rate for this clone was calculated as  $2 \times 10^{-3} \text{ s}^{-1}$ . The affinity of 1082C03 was calculated as 20 nM, assuming 100% activity of the scFv. The 5 scFvs with the highest affinities as scFvs are given in Table 8.

TABLE 8

Identification of 5 antibodies to membrane-bound BLyS that have the highest affinities as scFvs	
Antibody	Affinity ( $K_D$ )
1079F11	5 nM
1079E02	10 nM
1082G02	6 nM
1082H08	1 nM
1099D03	4 nM

## Example 19

## Recognition of Mouse Membrane-Bound B Lymphocyte Stimulator

The ability of the 5 scFvs listed in Table 8 to also recognize murine membrane-bound B Lymphocyte Stimulator was determined using a competition ELISA. This assay assesses the ability of test phage scFvs to bind to the membrane-bound form of B Lymphocyte Stimulator on the murine cell line, P388, plasma membranes in the presence of different forms of competing human B Lymphocyte Stimulator. Competing B Lymphocyte Stimulator was either presented as the His-tagged form of B Lymphocyte Stimulator, or soluble B Lymphocyte Stimulator. ScFvs that recognize mouse membrane-bound B Lymphocyte Stimulator would give an ELISA signal on the P388 plasma membranes that is competed out by pre-incubation with His-tagged B Lymphocyte Stimulator but not by pre-incubation with soluble B Lymphocyte Stimulator.

## Maintenance of P388.D1 Cells and Preparation of Plasma Membranes

P388.D1 cells are a mouse monocyte-macrophage like cell line. They were cultured in L-15 medium supplemented

with 2 mM L-glutamine, 10% CS, 10 U penicillin, 100 g/ml streptomycin (all reagents from Sigma). Cells were split 1:4 every 3–4 days to maintain a cell density of  $2\text{--}8 \times 10^5$  per ml. A fresh aliquot of cells was thawed from liquid nitrogen every 6 weeks. Plasma membrane fractions were prepared as described in Example 2.

#### Competition ELISA

P388 plasma membranes (50  $\mu$ l per well) were coated at 10  $\mu$ g/ml in PBS onto Falcon 96-well plates overnight at 4° C. The method is otherwise essentially as described Example 16.

The results for 3 clones, 1079E02, 1082H08 and 1099D03 are shown in FIG. 16. All 3 scFvs recognize P388 plasma membranes. This binding is competed out in the presence of HIS-tagged B Lymphocyte Stimulator (HIS-B Lymphocyte Stimulator) but not in the presence of biotinylated B Lymphocyte Stimulator (bio-B Lymphocyte Stimulator). This confirms that these scFvs also recognize the membrane-bound form but not the soluble form of mouse B Lymphocyte Stimulator.

#### Example 20

##### Conversion of scFvs to IgG1 Format

The VH domain and the VL domains of scFvs that we wished to convert into IgG molecules were cloned into vectors containing the nucleotide sequences of the appropriate heavy (human IgG1) or light chain (human kappa or human lambda) constant regions such that a complete heavy or light chain molecule could be expressed from these vectors when transfected into an appropriate host cell. Further, when cloned heavy and light chains are both expressed in one cell line (from either one or two vectors), they can assemble into a complete functional antibody molecule that is secreted into the cell culture medium. Methods for converting scFvs into conventional antibody molecules are well known within the art.

##### Generation of NSO Cell Lines Expressing Anti-B Lymphocyte Stimulator Antibodies (IgG1)

Plasmids containing the heavy and light chains were separately linearized using the Pvu 1 restriction enzyme. The linearized DNAs were purified by phenol-chloroform extraction followed by ethanol precipitation and then resuspended in H<sub>2</sub>O. NSO cells ( $10^7$ ) from a growing culture were electroporated (0.25 kV and 975  $\mu$ l) in PBS with 12.5  $\mu$ g linearized heavy chain plasmid DNA and 37.5  $\mu$ g linearized light chain DNA. The cells were washed in 20 ml non-selective medium (10% FCS in DMEM supplemented with 6 mM glutamine, amino acids and penicillin/streptomycin) and then transferred in 12.5 ml medium into a T75 cm<sup>2</sup> flask and incubated overnight at 37° C., 5% CO<sub>2</sub>/air. The day after transfection the cells were resuspended in selective medium containing 1 mg/ml geneticin and dispensed into 5x96-well plates at 200  $\mu$ l/well. After 18 days at 37° C. (5% CO<sub>2</sub>/air) the colony supernatants were screened by an ELISA that detects assembled human IgG in order to identify colonies expressing IgG. Approximately twenty positive colonies were expanded and adapted to growth in serum-free, selective medium. Duplicate T25 cm<sup>2</sup> flasks were set up. Cells from one flask were frozen down as a stock and cells in the second flask were grown to saturation. The productivity of

the saturated cultures was assessed by ELISA. The highest producing cell lines were then selected for large-scale antibody production.

The above procedure is exemplified for the 1006D08 anti-B Lymphocyte Stimulator antibody constructs. Following electroporation and selection of NSO cells, supernatants from ninety-three wells each containing a single colony were screened by ELISA to detect assembled IgG1 antibody. Twenty-seven of the supernatants were identified as containing IgG. The colonies from 24 of the positive wells were transferred to 1 ml selective medium in a 24-well plate and allowed to grow for 2 days. The 1 ml cultures of cells were then added to 4 ml selective medium containing reduced serum (0.5% FCS) in a T25 cm<sup>2</sup> flask. When the cultures reached confluency 1 ml cells were diluted in 4 ml selective, serum-free medium in a T25 cm<sup>2</sup> flask. At confluency this subculture regime was repeated again. Finally 1 ml cells from the culture containing 0.1% FCS was diluted with 9 ml serum-free, selective medium and divided into 2xT25 cm<sup>2</sup> to form the saturated and stock cultures. The stock cultures were frozen down and stored in liquid nitrogen once the cultures were confluent. The saturation culture was grown until the viability of the culture was <10%.

Twenty-three out of the 24 colonies originally expanded were successfully adapted to growth in serum-free medium. The productivity of these serum-free adapted cell lines ranged from 0.3 to 17  $\mu$ g/ml by ELISA quantification of the saturated, 5 ml serum-free cultures. The 1006D08-32 cell line produced 17  $\mu$ g/ml.

##### Large-Scale IgG Production

The highest-producing cell lines were revived from frozen stocks and then expanded to 400 ml in selective, serum-free medium in 2 liter roller bottles. The cells were grown at 37° C. and rolled at 4 rpm with the headspace being re-equilibrated with 5% CO<sub>2</sub>/air every 2–3 days. Finally the culture was expanded to a 4 liter volume by the addition of serum-free medium without selection (400 ml per 2 liter roller bottle). The cultures were then grown to saturation.

This procedure is exemplified by the production of 1006D08 antibody from the 1006D08-32 cell line. The frozen stock of 1006D08-32 was revived into a T25 cm<sup>2</sup> containing 5 ml serum-free medium containing 1 mg/ml geneticin and grown at 37° C. in 5% CO<sub>2</sub>/air incubator. After two days growth the culture was diluted with 7.5 ml fresh medium and transferred to a T75 cm<sup>2</sup> flask. After a further three days in the incubator the cells were transferred to 130 ml selective medium and transferred to a 2 liter roller bottle. After three days growth the cells were diluted with 500 ml selective medium and split into 2x2 liter roller bottles. After another 2 days 100 ml fresh selective medium was added to each roller. Finally the next day the culture was expanded to a total volume of 4 liters with non-selective medium and divided into 10x2 liter roller bottles. After three days the medium was supplemented with 6 mM glutamine. The cells were grown for 17 days from the final subculture into a 4 liter volume. The cells grew up to  $3 \times 10^7$  cells/ml before viability declined to <0.2x10<sup>7</sup> cells/ml. At this low viability the culture supernatants were harvested. ELISA analysis indicated that the culture supernatant contained 33  $\mu$ g/ml IgG. Hence, the 4 liter culture contained 132 mg IgG.

##### IgG Purification

The purification of the IgG from the fermentation broth is performed using a combination of conventional techniques

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commonly used for antibody purification. Typically the culture harvest is clarified to remove cells and cellular debris prior to starting the purification scheme. This would normally be achieved using either centrifugation or filtration of the harvest. Following clarification, the antibody would typically be captured and significantly purified using affinity chromatography on Protein A Sepharose. The antibody is bound to Protein A Sepharose at basic pH and, following washing of the matrix, is eluted by a reduction of the pH. Further purification of the antibody is then achieved by gel filtration. As well as removing components with different molecular weights from the antibody this step can also be used to buffer exchange into the desired final formulation buffer.

#### Purification of 1006D08 IgG1

The harvest was clarified by sequential filtration through 0.5  $\mu\text{m}$  and 0.22  $\mu\text{m}$  filters. Clarified harvest was then applied to a column of recombinant Protein A Sepharose equilibrated at pH 8.0 and washed with the equilibration buffer. 1006D08 antibody was eluted from the Protein A Sepharose by application of a buffer at pH 3.5. The collected antibody containing eluate was then neutralized to pH 7.4 by the addition of pH 8.0 buffer. The neutralized eluate was concentrated by ultrafiltration using a 30 kDa cut off membrane. Concentrated material was then purified by Sephacryl S300HR gel filtration using phosphate buffered saline as the mobile phase. The final monomeric IgG1 fraction from the gel filtration column was then concentrated to the desired formulation concentration by ultrafiltration using a 30 kDa cut off membrane. The final product was filtered through a 0.22  $\mu\text{m}$  filter.

#### Example 21

##### Antibody Neutralization of Murine Splenocyte Proliferation as Measured by 3HdT Incorporation

To determine if an antibody inhibited B Lymphocyte Stimulator mediated B cell proliferation, a splenocyte proliferation assay was performed. Briefly, murine splenocytes were isolated by flushing spleen with complete medium using a 25 g needle and 10 ml of complete medium (RPMI 1640 with 10% FBS containing 100 U/ml penicillin, 100  $\mu\text{g}/\text{ml}$  streptomycin, 4 mM glutamine,  $5 \times 10^{-5}\text{M}$   $\beta$ -mercaptoethanol). The cells were passed through a 100 micron nylon filter to remove cell clumps. The cell suspension was then ficoll at 400g for 25 minutes at room temperature (one 15 ml conical tube/spleen; 3 ml ficol, 10 ml cell suspension/spleen; Ficoll 1083 from Sigma). The recovered cells were washed 3 times in complete medium and counted. Recovered cells were then diluted to a concentration of  $3 \times 10^6/\text{ml}$  in complete medium containing a  $3 \times$  concentration of SAC ( $3 \times = 1:33,333$  dilution of stock) (*Staph. aureus* Cowan strain; Calbiochem).

For each antibody, 50 microliters of antibody dilutions at 30  $\mu\text{g}/\text{ml}$ , 3.0  $\mu\text{g}/\text{ml}$ , and 0.3  $\mu\text{g}/\text{ml}$  concentrations were aliquotted into individual wells of a 96 well plate in triplicate. Suitable positive controls, such as, for example monoclonal antibody 15C10, were also used. Medium containing no antibody (and human isotype controls (purchased commercially) when necessary) were used as negative controls.

B Lymphocyte Stimulator protein was diluted in complete medium to concentrations of 300 ng/ml, 90 ng/ml and 30 ng/ml. 50 microliters of each of the B Lymphocyte Stimu-

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lator dilutions were then added to the antibody dilution series in the plates. The plate containing the antibody and B Lymphocyte Stimulator dilutions are then incubated for 30 minutes at  $37^\circ\text{C}$ , 5%  $\text{CO}_2$ , after which 50 microliters of the splenocyte cell suspension containing SAC was added to all wells. The plates were then incubated for 72 hours ( $37^\circ\text{C}$ , 5%  $\text{CO}_2$ ).

After 72 hours, each well was supplemented with 50  $\mu\text{l}$  of complete medium containing 0.5  $\mu\text{Ci}$  of  $^3\text{H}$ -thymidine (6.7 Ci/mM; Amersham) and cells were incubated for an additional 20-24 hours at ( $37^\circ\text{C}$ , 5%  $\text{CO}_2$ ). Following incubation cells were harvested using a Tomtec Cell Harvester and filters counted in a TopCount Scintillation counter (Packard).

#### Example 22

##### Human B cell Proliferation Assay for In Vitro Screening of B Lymphocyte Stimulator Antagonist Molecules

The bioassay for assessing the effects of putative B Lymphocyte Stimulator antagonists was performed in triplicate in 96 well format by mixing equal volumes of B Lymphocyte Stimulator, responder cells, and putative antagonist each of which is prepared as a  $3 \times$  stock reagent.

B-lymphocytes were purified from human tonsil by MACS (anti-CD3 depletion), washed, and resuspended in complete medium (CM) (RPMI 1640 with 10% FBS containing 100 U/ml penicillin, 100  $\mu\text{g}/\text{ml}$  streptomycin, 4 mM glutamine,  $5 \times 10^{-5}\text{M}$   $\beta$ -mercaptoethanol) at a concentration of  $3 \times 10^6$  cells/mL. *Staphylococcus aureus*, Cowan 1 (SAC, CalBiochem) was added to cells at  $3 \times$  concentration ( $3 \times = 1:33,333$  dilution of stock).

Meanwhile, eight serial dilutions (3-fold) of potential antagonist were prepared in CM such that the diluted antagonists are at  $3 \times$  the final concentrations to be tested in the assay. Antibodies are routinely tested starting at a final concentration of 10  $\mu\text{g}/\text{ml}$  and going down to about 1.5 ng/mL.

Human rB Lymphocyte Stimulator was prepared in CM to  $3 \times$  concentration ( $3 \times = 300$  ng/mL, 30  $\mu\text{g}/\text{ml}$ , and 3 ng/mL) in CM. Potential inhibitors were routinely tested at several concentrations of B Lymphocyte Stimulator to avoid false negatives due to unexpectedly low affinity or antagonist concentration.

Fifty microliters of diluted antagonist and 50  $\mu\text{L}$  of diluted B Lymphocyte Stimulator were added to the putative antagonist dilution series.

Cells were then incubated for 72 hours ( $37^\circ\text{C}$ , 5%  $\text{CO}_2$ ) in a fully humidified chamber. After 72 hrs., the cells were supplemented with 0.5  $\mu\text{Ci}$  of  $^3\text{H}$ -thymidine (6.7 Ci/mmol) and incubated for an additional 24 hours. Plates were harvested using a Tomtec Cell Harvester and filters counted in a TopCount Scintillation counter (Packard).

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in this application is incorporated in their entireties herein by reference. Further, the sequences disclosed herein are also disclosed in U.S. Provisional Application 60/212,210 filed Jun. 16, 2000 the contents of which are incorporated in their entireties herein by reference.

TABLE 1

Clone ID	mFc SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	seqs that immunospecifically bind to H2S <sub>2</sub>			AAs of VH CDR2	AAs of VH CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)	VH CDR3 Sequence (SEQ ID NO)
1000F12S	1	138-248	160-173	22,189-195	228-237	1-122	26-35	30-66	99-111	1000V12S	1	30-66	1000V12S	1	1000V12S
1000F13S	2	138-248	160-173	22,189-195	228-237	1-122	26-35	30-66	99-111	1000V13S	2	30-66	1000V13S	2	1000V13S
1000F14S	3	144-254	166-177	195-201	234-243	1-128	26-35	32-69	102-127	1000V14S	3	32-69	1000V14S	3	1000V14S
1000F15S	4	148-258	169-179	195-201	234-243	1-132	26-35	30-66	99-121	1000V15S	4	30-66	1000V15S	4	1000V15S
1000F16S	5	142-249	163-173	189-195	228-238	1-126	26-35	30-66	99-115	1000V16S	5	30-66	1000V16S	5	1000V16S
1000F17S	6	137-251	160-173	189-195	228-239	1-121	26-35	30-66	99-113	1000V17S	6	30-66	1000V17S	6	1000V17S
1000F18S	7	140-250	164-174	190-196	229-239	1-124	26-35	30-66	99-113	1000V18S	7	30-66	1000V18S	7	1000V18S
1000F19S	8	142-256	168-181	197-203	236-245	1-129	26-35	30-66	99-114	1000V19S	8	30-66	1000V19S	8	1000V19S
1000F20S	9	142-256	168-181	197-203	236-245	1-129	26-35	30-66	99-114	1000V20S	9	30-66	1000V20S	9	1000V20S
1000F21S	10	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V21S	10	30-66	1000V21S	10	1000V21S
1000F22S	11	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V22S	11	30-66	1000V22S	11	1000V22S
1000F23S	12	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V23S	12	30-66	1000V23S	12	1000V23S
1000F24S	13	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V24S	13	30-66	1000V24S	13	1000V24S
1000F25S	14	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V25S	14	30-66	1000V25S	14	1000V25S
1000F26S	15	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V26S	15	30-66	1000V26S	15	1000V26S
1000F27S	16	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V27S	16	30-66	1000V27S	16	1000V27S
1000F28S	17	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V28S	17	30-66	1000V28S	17	1000V28S
1000F29S	18	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V29S	18	30-66	1000V29S	18	1000V29S
1000F30S	19	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V30S	19	30-66	1000V30S	19	1000V30S
1000F31S	20	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V31S	20	30-66	1000V31S	20	1000V31S
1000F32S	21	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V32S	21	30-66	1000V32S	21	1000V32S
1000F33S	22	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V33S	22	30-66	1000V33S	22	1000V33S
1000F34S	23	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V34S	23	30-66	1000V34S	23	1000V34S
1000F35S	24	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V35S	24	30-66	1000V35S	24	1000V35S
1000F36S	25	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V36S	25	30-66	1000V36S	25	1000V36S
1000F37S	26	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V37S	26	30-66	1000V37S	26	1000V37S
1000F38S	27	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V38S	27	30-66	1000V38S	27	1000V38S
1000F39S	28	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V39S	28	30-66	1000V39S	28	1000V39S
1000F40S	29	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V40S	29	30-66	1000V40S	29	1000V40S
1000F41S	30	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V41S	30	30-66	1000V41S	30	1000V41S
1000F42S	31	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V42S	31	30-66	1000V42S	31	1000V42S
1000F43S	32	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V43S	32	30-66	1000V43S	32	1000V43S
1000F44S	33	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V44S	33	30-66	1000V44S	33	1000V44S
1000F45S	34	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V45S	34	30-66	1000V45S	34	1000V45S
1000F46S	35	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V46S	35	30-66	1000V46S	35	1000V46S
1000F47S	36	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V47S	36	30-66	1000V47S	36	1000V47S
1000F48S	37	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V48S	37	30-66	1000V48S	37	1000V48S
1000F49S	38	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V49S	38	30-66	1000V49S	38	1000V49S
1000F50S	39	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V50S	39	30-66	1000V50S	39	1000V50S
1000F51S	40	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V51S	40	30-66	1000V51S	40	1000V51S
1000F52S	41	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V52S	41	30-66	1000V52S	41	1000V52S
1000F53S	42	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V53S	42	30-66	1000V53S	42	1000V53S
1000F54S	43	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V54S	43	30-66	1000V54S	43	1000V54S
1000F55S	44	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V55S	44	30-66	1000V55S	44	1000V55S
1000F56S	45	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V56S	45	30-66	1000V56S	45	1000V56S
1000F57S	46	141-251	166-177	193-199	232-240	1-125	26-35	30-66	99-114	1000V57S	46	30-66	1000V57S	46	1000V57S

TABLE 1—continued

Clone ID	seq# SEQ ID NO	seqs that Immunospecifically Bind to B10.S									
		AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	Sequence (SEQ ID NO)	
08B7A07	47	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2227)	
08B7A08	48	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLCRPH (SEQ ID NO: 2228)	
08B7A09	49	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7B02	50	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7B03	51	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7B04	52	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7B05	53	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7B06	54	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7B08	55	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7B09	56	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7C02	57	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7C05	58	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7C06	59	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7C07	60	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7C08	61	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7D01	62	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7D02	63	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7D03	64	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7D05	65	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7D07	67	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7D08	68	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7E04	69	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7E10	70	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7F02	71	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7F04	72	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7F05	73	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7F07	74	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7F08	75	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7F09	76	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7G05	77	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7G06	78	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7G07	79	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7G08	80	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B7H02	81	140-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B8A01	82	137-244	160-170	186-192	223-233	1-121	26-35	50-66	99-110	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B8A02	83	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B8A03	84	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B8A04	85	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B8A06	86	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B8A09	87	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B8A10	88	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B8A11	89	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B8A12	90	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B8B01	91	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	
08B8B02	92	141-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDILSVLPKPV (SEQ ID NO: 2228)	

scFv SEQ ID										scFvs that Immunoselectively Bind to B16S									
Clone ID																			
AA of VL										AA of VH									
AA of VL CDR3										AA of VH CDR3									
AA of VL CDR1										AA of VH CDR1									
AA of VL CDR2										AA of VH CDR2									
AA of VL CDR4										AA of VH CDR4									
AA of VL CDR5										AA of VH CDR5									
AA of VL CDR6										AA of VH CDR6									
AA of VL CDR7										AA of VH CDR7									
AA of VL CDR8										AA of VH CDR8									
AA of VL CDR9										AA of VH CDR9									
AA of VL CDR10										AA of VH CDR10									
AA of VL CDR11										AA of VH CDR11									
AA of VL CDR12										AA of VH CDR12									
AA of VL CDR13										AA of VH CDR13									
AA of VL CDR14										AA of VH CDR14									
AA of VL CDR15										AA of VH CDR15									
AA of VL CDR16										AA of VH CDR16									
AA of VL CDR17										AA of VH CDR17									
AA of VL CDR18										AA of VH CDR18									
AA of VL CDR19																			

TABLE 1-continued

Clone ID	seqFv SEQ ID NO	seqFv that Immunogenetically Bind to B1a5									
		AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	AAs of VH CDR3 Sequence (SEQ ID NO)	AAs of VH CDR3	
109-3C08	141	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2254)	99-114	
109-3C12	142	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3D06	143	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2256)	99-114	
109-3D07	144	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3D09	145	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2255)	99-114	
109-3D10	146	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2256)	99-114	
109-3D11	147	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3E01	148	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2254)	99-114	
109-3E02	149	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3E03	150	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2255)	99-114	
109-3E04	151	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2248)	99-114	
109-3E10	152	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3E11	153	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2257)	99-114	
109-3F01	154	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3F02	155	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3F03	156	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3F07	157	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3F08	158	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3F11	159	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3F12	160	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3G01	161	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3G02	162	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3G10	163	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3H01	164	137-244	160-170	186-192	328-233	1-121	50-66	99-110	ASYLTSLSLDN (SEQ ID NO: 2265)	3354	
109-3H06	165	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2248)	99-114	
109-3A09	166	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3A10	167	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3B02	168	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3B03	169	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3B05	170	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3B06	171	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3B12	172	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3D10	173	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3D12	174	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3D13	175	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2242)	99-114	
109-3D05	176	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3D05	177	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2245)	99-114	
109-3D08	178	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2245)	99-114	
109-3D10	179	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3D12	180	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3E02	181	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3E03	182	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2137)	99-114	
109-3E05	183	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2287)	99-114	
109-3E08	184	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2283)	99-114	
109-3E10	185	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2251)	99-114	
109-3F01	186	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2251)	99-114	
109-3F03	187	141-251	166-177	193-199	332-240	1-125	50-66	99-114	PFYDILSVVQVNSL (SEQ ID NO: 2251)	99-114	

### scFvs that Immunospecifically Bind to BLyS

[illegible]



Issue ID	Seq#	Seq ID	AAs of VL	AAs of VL	VL CD3	AAs of VH	CD81	AAs of VH	AAs of VH	VH CD3 Sequence (Seq ID No.)
093H09	233	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2391)
093G06	234	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2392)
093G06	235	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2393)
093G06	236	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2394)
093G06	237	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2395)
093G06	238	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2396)
093G06	239	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2397)
093G06	240	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2398)
093G06	241	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2399)
093G06	242	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2400)
093G06	243	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2401)
093G06	244	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2402)
093G06	245	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2403)
093G06	246	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2404)
093G06	247	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2405)
093G06	248	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2406)
093G06	249	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2407)
093G06	250	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2408)
093G06	251	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2409)
093G06	252	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2410)
093G06	253	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2411)
093G06	254	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2412)
093G06	255	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2413)
093G06	256	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2414)
093G06	257	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2415)
093G06	258	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2416)
093G06	259	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2417)
093G06	260	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2418)
093G06	261	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2419)
093G06	262	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2420)
093G06	263	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2421)
093G06	264	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2422)
093G06	265	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2423)
093G06	266	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2424)
093G06	267	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2425)
093G06	268	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2426)
093G06	269	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2427)
093G06	270	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2428)
093G06	271	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2429)
093G06	272	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2430)
093G06	273	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2431)
093G06	274	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2432)
093G06	275	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2433)
093G06	276	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2434)
093G06	277	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2435)
093G06	278	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2436)
093G06	279	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2437)
093G06	280	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2438)
093G06	281	141-251	166-177	193-199	232-240	1-25	36-35	50-66	99-114	PFYDILSYVQVDFV (Seq ID No.: 2439)

TABLE 1-continued

[illegible]

### scFvs that Immunospecifically Bind to BLyS

Issue ID	sEP-SEQ ID	AA's of VL	AA's of VL CDR1	AA's of VL CDR2	AA's of VL CDR3	AA's of VH	AA's of VH CDR1	AA's of VH CDR2	AA's of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
16C11	329	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFHPSHSL (SEQ ID NO: 2147)
18S401	330	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFHPSHSL (SEQ ID NO: 2147)
18S402	331	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFHPSHSL (SEQ ID NO: 2639)
18S403	332	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFHPSHSL (SEQ ID NO: 2561)
18S404	333	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFF (SEQ ID NO: 2550)
18S405	334	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFF (SEQ ID NO: 2659)
18S406	335	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2611)
18S407	336	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2660)
18S408	337	139-248	162-172	188-194	227-237	1-122	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2399)
18S409	338	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2363)
18S410	339	139-248	162-172	188-194	227-237	1-122	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2466)
18S411	340	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2392)
18S412	341	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2638)
18S413	342	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2589)
18S414	343	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2545)
18S415	344	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2433)
18S416	345	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2372)
18S417	346	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2400)
18S418	347	139-249	163-173	189-194	227-237	1-122	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2491)
18S419	348	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2373)
18S420	349	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2545)
18S421	350	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2470)
18S422	351	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2430)
18S423	352	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2400)
18S424	353	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2471)
18S425	354	139-249	163-173	189-194	227-237	1-122	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2600)
18S426	355	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2548)
18S427	356	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2713)
18S428	357	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDLPFLAPLFL (SEQ ID NO: 2646)
18S429	358	139-249	163-1							

TABLE 1-continued

Clone ID	seqV, SEQ ID NO	seqV that immunospecifically bind to HLA5									
		AA# of VL	AA# of VL CDR1	AA# of VL CDR2	AA# of VL CDR3	AA# of VH	AA# of VH CDR1	AA# of VH CDR2	AA# of VH CDR3	Sequence (SEQ ID NO)	
D8SF01	376	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2351)	
D8SF02	377	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2352)	
D8SF03	378	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2353)	
D8SF04	379	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2354)	
D8SF05	380	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2355)	
D8SF06	381	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2356)	
D8SF07	382	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2357)	
D8SF08	383	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2358)	
D8SF09	384	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2359)	
D8SF10	385	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2360)	
D8SF11	386	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2361)	
D8SF12	387	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2362)	
D8SF13	388	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2363)	
D8SG02	389	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2364)	
D8SG03	390	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2365)	
D8SG04	391	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2366)	
D8SG05	392	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2367)	
D8SG06	393	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2368)	
D8SG07	394	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2369)	
D8SG11	396	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2370)	
D8SH10	397	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2371)	
D8SH11	398	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2372)	
D8SH12	399	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2373)	
D8SH13	400	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2374)	
D8SH14	401	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2375)	
D8SH15	402	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2376)	
D8SH16	403	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2377)	
D8SH17	404	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2378)	
D8SH18	405	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2379)	
D8SH19	406	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2380)	
D8SH20	407	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2381)	
D8SH21	408	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2382)	
D8SH22	409	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2383)	
D8SH23	410	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2384)	
D8SH24	411	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2385)	
D8SH25	412	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2386)	
D8SH26	413	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2387)	
D8SH27	414	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2388)	
D8SH28	415	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2389)	
D8SH29	416	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2390)	
D8SH30	417	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2391)	
D8SH31	418	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2392)	
D8SH32	419	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2393)	
D8SH33	420	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2394)	
D8SH34	421	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2395)	
D8SH35	422	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILLFPPSLIF (SEQ ID NO: 2396)	

TABLE 1-continued

Clone ID	seqV SEQ ID NO	AAs of VL	VL CDR1	AAs of VL CDR2	VL CDR3	seqs that Immunospecifically Bind to B1ys.				AAs of VH	VH CDR3	seqV SEQ ID NO
						AAs of VH	AAs of CDR1	AAs of VH	AAs of CDR1			
0806D04	423	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SVYLLFPYATVYD (SEQ ID NO: 2697)		
0806D05	424	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYAPLSD (SEQ ID NO: 2461)		
0806D06	425	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPATPLSD (SEQ ID NO: 2179)		
0806D07	426	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYTHLTF (SEQ ID NO: 2365)		
0806D08	427	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPHTSLTF (SEQ ID NO: 2473)		
0806D09	428	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPNHEMP (SEQ ID NO: 2665)		
0806D10	429	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPNTHLTF (SEQ ID NO: 2487)		
0806D11	430	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPNTHLTF (SEQ ID NO: 2587)		
0806D12	431	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2669)		
0806D13	432	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPDHALGS (SEQ ID NO: 2198)		
0806D14	433	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPDHALGS (SEQ ID NO: 2567)		
0806D15	434	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2398)		
0806D16	435	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2599)		
0806D17	436	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2650)		
0806D18	437	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2572)		
0806D19	438	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2714)		
0806D20	439	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2549)		
0806D21	440	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2643)		
0806D22	441	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2489)		
0806D23	442	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2633)		
0806D24	443	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2561)		
0806D25	444	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2454)		
0806D26	445	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2573)		
0806D27	446	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2407)		
0806D28	447	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2448)		
0806D29	448	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2385)		
0806D30	449	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SKDILLFPYATLHF (SEQ ID NO: 2391)		
0806D31	450	139-249	163-173	189-195	228-238	1-123						

TABLE 1-continued

Gene ID	gSV-SEQ ID	AA's of VL	VL CDR1	AA's of VL CDR2	VL CDR3	AA's of VH	AA's of VH CDR1	AA's of VH CDR2	AA's of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
898B011	470	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPNSPLP (SEQ ID NO: 2388)
898B012	471	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFYGMV (SEQ ID NO: 2133)
898B02	472	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFGPLP (SEQ ID NO: 2511)
898B03	473	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2532)
898B04	474	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2722)
898B06	475	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2683)
898B07	476	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B09	477	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2546)
898B10	478	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2344)
898B11	479	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2717)
898B12	480	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2549)
898B13	481	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2346)
898B14	482	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B15	483	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B16	484	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B17	485	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B18	486	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B19	487	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B20	488	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B21	489	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B22	490	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B23	491	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B24	492	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B25	493	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B26	494	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B27	495	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B28	496	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B29	497	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B30	498	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLLPFLP (SEQ ID NO: 2677)
898B31	499	139-249	163-173	189-195	228-238	1-123	26-35	50-66</		

TABLE 1 - continued

Seqs that Immunogenically Bind to B15s

Clone ID	Seq ID NO	AA's of VL	AA's of VL CDR1	AA's of VL CDR2	AA's of VH	AA's of VH CDR1	AA's of VH CDR2	AA's of VH CDR3	Seq ID NO
109A06	517	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2600)	99-112
109A07	518	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2479)	99-112
109A08	519	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2480)	99-112
109A09	520	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2481)	99-112
109A10	521	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2482)	99-112
109A11	522	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2483)	99-112
109A12	523	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2484)	99-112
109A13	524	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2485)	99-112
109A14	525	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2486)	99-112
109A15	526	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2487)	99-112
109A16	527	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2488)	99-112
109A17	528	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2489)	99-112
109A18	529	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2490)	99-112
109A19	530	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2491)	99-112
109A20	531	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2492)	99-112
109A21	532	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2493)	99-112
109A22	533	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2494)	99-112
109A23	534	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2495)	99-112
109A24	535	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2496)	99-112
109A25	536	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2497)	99-112
109A26	537	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2498)	99-112
109A27	538	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2499)	99-112
109A28	539	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2500)	99-112
109A29	540	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2501)	99-112
109A30	541	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2502)	99-112
109A31	542	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2503)	99-112
109A32	543	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2504)	99-112
109A33	544	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2505)	99-112
109A34	545	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2506)	99-112
109A35	546	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2507)	99-112
109A36	547	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2508)	99-112
109A37	548	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2509)	99-112
109A38	549	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2510)	99-112
109A39	550	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2511)	99-112
109A40	551	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2512)	99-112
109A41	552	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2513)	99-112
109A42	553	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2514)	99-112
109A43	554	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2515)	99-112
109A44	555	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2516)	99-112
109A45	556	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2517)	99-112
109A46	557	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2518)	99-112
109A47	558	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2519)	99-112
109A48	559	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2520)	99-112
109A49	560	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2521)	99-112
109A50	561	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2522)	99-112
109A51	562	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2523)	99-112
109A52	563	139-249	163-173	189-195	238-238	1-123	26-35	SRDLFFPYPLSF (SEQ ID NO: 2524)	99-112

TABLE I-continued

Clone ID	scfV SEQ ID	AA# of VL	AA# of VL CDR1	AA# of VL CDR2	AA# of VL CDR3	VH	AA# of VH CDR1	AA# of VH CDR2	AA# of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
564	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPRDPLF (SEQ ID NO: 2393)	
565	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2633)	
566	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2472)	
567	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2660)	
568	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2460)	
569	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2356)	
570	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2343)	
571	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2669)	
572	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2593)	
573	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2594)	
574	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2541)	
575	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2581)	
576	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2361)	
577	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2393)	
578	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2475)	
579	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2352)	
580	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2440)	
581	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2440)	
582	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2440)	
583	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2440)	
584	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2440)	
585	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2378)	
586	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2531)	
587	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2583)	
588	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2344)	
589	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2415)	
590	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2600)	
591	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2673)	
592	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2673)	
593	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2443)	
594	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2606)	
595	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2606)	
596	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2606)	
597	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2606)	
598	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2606)	
599	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2456)	
600	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2645)	
601	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2719)	
602	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2660)	
603	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2352)	
604	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2547)	
605	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2576)	
606	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2661)	
607	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2607)	
608	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2361)	
609	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2460)	
610	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SDLLFLPHEPLAF (SEQ ID NO: 2599)	



[illegible]

TABLE 1—continued

gG16 that Immunoreactively Bind to B185									
Clone ID	gG1 SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3
I104E11	658	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E12	659	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E13	660	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E14	661	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E15	662	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E16	663	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E17	664	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E18	665	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E19	666	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E20	667	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E21	668	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E22	669	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E23	670	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E24	671	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E25	672	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E26	673	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E27	674	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E28	675	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E29	676	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E30	677	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E31	678	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E32	679	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E33	680	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E34	681	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E35	682	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E36	683	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E37	684	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E38	685	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E39	686	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E40	687	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E41	688	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E42	689	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E43	690	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E44	691	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E45	692	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E46	693	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E47	694	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E48	695	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E49	696	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E50	697	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E51	698	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E52	699	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E53	700	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E54	701	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E55	702	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E56	703	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112
I104E57	704	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112

TABLE 1-continued

αFα that Immunogenically Bind to H1A5										
Close ID	sαF SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I05F12	705	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2604)
I05G03	706	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2370)
I05G08	707	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2366)
I05G09	708	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2364)
I05G10	709	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2645)
I05G11	710	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2501)
I05G12	711	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2509)
I05G13	712	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2509)
I05G14	713	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2671)
I05G15	714	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2564)
I05G16	715	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2533)
I05G17	716	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2420)
I05G18	717	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2420)
I05G19	718	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2420)
I05G20	719	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2420)
I05G21	720	137-247	161-171	187-193	226-236	1-121	24-33	48-64	97-110	SRDILFFHYPLV (SEQ ID NO: 2594)
I05G22	721	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2510)
I05G23	722	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G24	723	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G25	724	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G26	725	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G27	726	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G28	727	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G29	728	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G30	729	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G31	730	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G32	731	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G33	732	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G34	733	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G35	734	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G36	735	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G37	736	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G38	737	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G39	738	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G40	739	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G41	740	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G42	741	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G43	742	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G44	743	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G45	744	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G46	745	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G47	746	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G48	747	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G49	748	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G50	749	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G51	750	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)
I05G52	751	139-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDILFFHYPLV (SEQ ID NO: 2684)

TABLE 1—continued

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TABLE 1-continued  
αβ TCR that Immunogenically Bind to HLA-B\*57:01

Clone ID	scFV SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	HLA CDR3 Sequence (SEQ ID NO)
1114E01	799	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2435)
1114E02	800	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2437)
1114E03	801	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2438)
1114E11	802	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2439)
1114E12	803	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2440)
1114H06	804	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2441)
1114H09	805	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2442)
1115A02	806	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2443)
1115A07	807	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2444)
1115B10	808	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2445)
1115C05	809	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2446)
1115C06	810	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2447)
1115C08	811	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2448)
1115C12	812	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2449)
1115D07	813	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2450)
1115E09	814	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2451)
1115F06	815	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2452)
1115F07	816	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2453)
1115F12	817	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2454)
1115G04	818	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2455)
1115G05	819	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2456)
1115G08	820	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2457)
1115H04	821	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2458)
1115H05	822	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2459)
1115H09	823	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2460)
1115H07	824	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2461)
1116B01	825	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2462)
1116B12	826	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2463)
1116C06	827	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2464)
1116C07	828	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2465)
1116C08	829	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2466)
1116C09	830	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2467)
1116E01	831	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2468)
1116E11	832	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2469)
1116G05	833	139-249	163-173	189-195	238-238	1-123	26-35	50-66	99-112	SRDILLFQPEFLSP (SEQ ID NO: 2470)
1116G06	834	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DSGVDLLGLVYVYFEL (SEQ ID NO: 21364)
1116G07	835	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DSGVDLLGLVYVYFEL (SEQ ID NO: 21365)
1116G08	836	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DSGVDLLGLVYVYFEL (SEQ ID NO: 21366)
1116G09	837	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DSGVDLLGLVYVYFEL (SEQ ID NO: 21367)
1116H01	838	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-114	ATYDLTGLVYVYFEL (SEQ ID NO: 21368)
1116H02	839	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-114	ATYDLTGLVYVYFEL (SEQ ID NO: 21369)
1116H03	840	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-114	ATYDLTGLVYVYFEL (SEQ ID NO: 21370)
1116H04	841	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-114	ATYDLTGLVYVYFEL (SEQ ID NO: 21371)
1116H05	842	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-114	ATYDLTGLVYVYFEL (SEQ ID NO: 21372)
1116H06	843	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-114	ATYDLTGLVYVYFEL (SEQ ID NO: 21373)
1116H07	844	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-114	ATYDLTGLVYVYFEL (SEQ ID NO: 21374)
1116H08	845	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-114	ATYDLTGLVYVYFEL (SEQ ID NO: 21375)

TABLE 1-continued

[illegible]

TABLE 1-continued

Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR2	AAs of VL CDR3	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	scFv that Immunoselectively Bind to BLA5	VH CDR3 Sequence (SEQ ID NO)	VH CDR3 Sequence (SEQ ID NO)
1003A10	893	141-248	162-172	188-194	227-237	1-125	1-125	50-66	MEYDILGYGGYFDY (SEQ ID NO: 2179)	99-114
1003B03	894	140-251	163-172	192-198	231-240	1-124	26-35	50-66	RYDILGYGGYFDY (SEQ ID NO: 2179)	99-114
1003B04	895	138-248	162-172	188-194	227-237	1-124	26-34	49-65	RYGDFPYYYMAY (SEQ ID NO: 2852)	98-111
1003B09	896	142-249	163-173	189-195	228-238	1-122	25-35	50-66	DYDILGYGGYFDY (SEQ ID NO: 2135)	99-115
1003C01	897	140-251	164-176	192-198	231-241	1-124	26-34	49-65	ELGASVATGALDM (SEQ ID NO: 2174)	98-113
1003C02	898	140-252	164-176	192-198	231-241	1-125	26-35	50-66	GDYDILGYPAETQI (SEQ ID NO: 2854)	99-114
1003C03	899	141-250	164-174	190-196	229-239	1-125	26-35	50-66	RYDILGYGGYFDY (SEQ ID NO: 2179)	99-114
1003C12	900	141-248	162-172	188-194	227-237	1-125	26-35	50-66	RYDILGYGGYFDY (SEQ ID NO: 2179)	99-114
1003D04	901	139-250	162-174	190-196	229-239	1-125	26-35	50-66	ELGSSVATGALDM (SEQ ID NO: 2854)	99-114
1003E05	902	141-253	166-176	192-198	231-242	1-125	26-35	50-66	ELGSSVATGALDM (SEQ ID NO: 2854)	99-114
1003F01	903	140-251	163-176	192-198	231-240	1-124	26-34	49-65	RYGDFPYYYMAY (SEQ ID NO: 2755)	99-112
1003F02	904	140-251	163-175	191-197	230-240	1-123	26-35	50-66	GTGYDILGYMGAFTQ (SEQ ID NO: 2800)	99-116
1003G01	905	143-254	166-179	195-201	234-241	1-127	26-35	50-66	GSYDILGYTGSPLDY (SEQ ID NO: 2766)	99-116
1003G05	906	143-254	166-179	195-201	234-241	1-127	26-35	50-66	DAQSYDILGYQVAFDY (SEQ ID NO: 2185)	99-117
1003G06	907	145-256	168-181	197-203	236-240	1-129	26-35	50-66	TYDILGYSRREFP (SEQ ID NO: 2940)	99-117
1003G11	908	144-251	165-175	191-197	230-240	1-128	26-35	50-66	ELGSSVATGALDM (SEQ ID NO: 2852)	99-113
1003H01	909	140-253	164-176	192-198	233-242	1-124	26-35	50-66	DYDILGYGGYFDY (SEQ ID NO: 2135)	99-115
1003H02	910	140-253	163-176	192-198	231-240	1-124	26-34	49-65	DYDILGYGGYFDY (SEQ ID NO: 2135)	99-115
1003H08	911	142-249	165-178	193-199	232-240	1-125	26-35	50-66	SHYDILGLNYTFDL (SEQ ID NO: 2166)	99-114
1003A01	912	141-249	162-172	188-194	227-237	1-125	26-35	50-66	SHYDILGLNYTFDL (SEQ ID NO: 2893)	99-114
1003A02	913	141-248	162-172	188-194	227-237	1-125	26-35	50-66	SHYDILGLNYTFDL (SEQ ID NO: 2166)	99-114
1003B01	914	141-248	162-172	188-194	227-237	1-125	26-35	50-65	TYDILGYGREFD (SEQ ID NO: 2860)	99-110
1003B09	915	137-247	159-172	188-194	227-236	1-121	26-35	50-65	SHYDILGLNYTFDL (SEQ ID NO: 2166)	99-114
1003B10	916	141-248	162-172	188-194	227-237	1-125	26-35	50-66	DLKYLDTGTHDAFDI (SEQ ID NO: 2890)	99-114
1003D02	917	141-251	163-175	193-199	232-240	1-125	26-35	50-66	GAYDILGYGGYFDY (SEQ ID NO: 2860)	99-113
1003D03	918	142-249	165-175	191-197	230-238	1-126	26-35	50-66	GAYDILGYGGYFDY (SEQ ID NO: 2860)	99-113
1003E01	919	142-249	165-175	191-197	230-238	1-126	26-35	50-66	SHYDILGLNYTFDL (SEQ ID NO: 2860)	99-114
1003E08	920	141-248	162-172	188-194	227-237	1-125	26-35	50-66	DYDILGYGGYFDY (SEQ ID NO: 2849)	99-117
1003F01	921	140-248	164-174	190-196	229-238	1-124	26-35	50-66	TYDILGYGREFD (SEQ ID NO: 2849)	99-110
1003F01	922	144-251	167-177	193-199	232-240	1-128	26-35	50-66	PSYDILGYLYFDY (SEQ ID NO: 2850)	99-113
1003F04	923	142-250	167-177	193-199	232-240	1-128	26-35	50-66	PSYDILGYLYFDY (SEQ ID NO: 2850)	99-113
1003F04	924	140-247	161-172	187-193	227-236	1-121	26-35	50-66	PSYDILGYLYFDY (SEQ ID NO: 2850)	99-113
1003F01	925	141-251	163-176	192-198	231-240	1-125	26-35	50-66	PSYDILGYLYFDY (SEQ ID NO: 2850)	99-113
1003G01	926	142-249	165-175	191-197	230-238	1-126	26-35	50-66	GAYDILGYTHDAFDI (SEQ ID NO: 2860)	99-113
1003H02	927	140-247	161-171	187-193	226-236	1-124	26-35	50-66	GYDILGYGNNFEP (SEQ ID NO: 2133)	99-111
1003H09	928	139-246	160-170	186-192	225-235	1-127	26-35	50-66	GYSSGRLGGPNNFEP (SEQ ID NO: 2967)	99-116
1006C09	929	141-251	163-176	193-199	232-242	1-127	26-35	50-66	GYDILGYTGLRDY (SEQ ID NO: 2792)	99-114
1006E01	931	143-253	165-178	194-200	233-242	1-129	26-35	50-66	NLDVWTLPTYYMAY (SEQ ID NO: 2965)	101-116
1006E02	932	143-250	166-176	192-198	231-239	1-127	26-35	50-66	MYDILGTHNEDY (SEQ ID NO: 2762)	101-113
1006R01	933	140-250	164-176	191-197	230-239	1-124	26-35	50-66	VSRLDILGTYTYGMDV (SEQ ID NO: 2817)	99-115
1006R02	934	142-253	167-178	192-198	231-242	1-126	26-35	50-66	GYSSGRLGGPNNFEP (SEQ ID NO: 2967)	99-116
1006R03	935	142-253	167-178	192-198	231-242	1-126	26-35	50-66	AGGYDILGTYTYGMDV (SEQ ID NO: 2877)	101-119
1006G04	936	146-253	170-185	193-199	232-242	1-130	26-35	50-66	RYDALDY (SEQ ID NO: 2920)	99-105
1006G04	937	132-239	153-163	170-185	218-228	1-110	26-35	50-66	RYDALDY (SEQ ID NO: 2920)	99-105
1006H01	938	146-253	167-177	193-199	232-242	1-130	26-35	50-66	GYSSGRLGGPNNFEP (SEQ ID NO: 2761)	99-116
1006H02	939	143-253	168-177	193-199	232-242	1-130	26-35	50-66	GYSSGRLGGPNNFEP (SEQ ID NO: 2761)	99-116

TABLE 1-continued

Close ID	seq. SEQ ID NO	seq. that Immunoreactively Bind to B10S									
		AAs of VL	AAs of VL CDR1	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)		
1007A01	940	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1007A08	941	139-249	163-176	192-198	239-238	1-125	26-35	99-114	SHYDLITGLNYYWYDF (SEQ ID NO: 2176)		
1007A11	942	140-250	163-175	191-197	230-239	1-124	26-35	99-113	ENYDLITGLYGFADF (SEQ ID NO: 2772)		
1007A12	943	144-251	163-175	191-197	230-240	1-128	26-35	99-113	ENYDLITGLYGFADF (SEQ ID NO: 2892)		
1007B04	944	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1007C04	945	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1007C08	946	142-249	163-173	189-195	238-238	1-126	26-35	99-115	BNLYCVSLTGYPGYGMDF (SEQ ID NO: 2800)		
1007C12	947	140-250	163-175	191-197	230-239	1-124	26-35	99-113	GYQYDLITGLYQGVYDF (SEQ ID NO: 2782)		
1007D07	948	140-250	163-175	187-193	236-236	1-124	26-35	99-113	GYQYDLITGLYQGVYDF (SEQ ID NO: 2857)		
1007D08	949	144-251	163-175	191-197	230-240	1-128	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2872)		
1007D09	950	141-248	162-172	188-194	237-237	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1007E01	951	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1007E11	952	144-251	163-175	192-197	230-240	1-128	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2741)		
1007F08	953	141-248	162-172	188-194	237-237	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1007G07	954	143-253	163-178	194-200	233-242	1-127	26-35	99-114	GRVYDLITGLYTHHGADF (SEQ ID NO: 2811)		
1007G08	955	141-251	163-176	192-198	231-240	1-125	26-35	99-113	SHYDLITGLNYYWYDF (SEQ ID NO: 2160)		
1007G09	956	142-252	164-177	193-199	232-241	1-126	26-35	99-115	DSGGYDLITGLYTFYDF (SEQ ID NO: 2847)		
1007H01	957	143-249	163-173	189-195	238-238	1-126	26-35	99-115	GVGYDLITGLYTWYGMDF (SEQ ID NO: 2805)		
1007H02	958	147-255	169-182	198-204	237-246	1-125	26-35	100-120	GVGYDLITGLYTWYGMDF (SEQ ID NO: 2875)		
1007H11	959	141-248	162-172	188-194	237-237	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2891)		
1008A02	960	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1008A05	961	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1008A06	962	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1008A07	963	141-251	163-173	189-195	238-238	1-126	26-35	99-113	DREYDLITGLYHAFDMF (SEQ ID NO: 2860)		
1008A12	964	146-256	163-173	188-194	237-237	1-124	26-35	99-113	ENYDLITGLYGFADF (SEQ ID NO: 2772)		
1008B02	965	141-248	162-172	188-194	237-237	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1008B04	966	143-253	163-178	194-200	233-242	1-127	26-35	99-114	DGSLITGLYTHYGMDF (SEQ ID NO: 2154)		
1008B05	967	141-248	162-172	188-194	237-237	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2160)		
1008B06	968	141-251	163-176	192-198	231-240	1-125	26-35	99-114	GRVYDLITGLYKGFYDF (SEQ ID NO: 2802)		
1008B07	969	140-247	163-173	189-195	238-238	1-124	26-35	99-113	ATYDNLITGLPYGMDF (SEQ ID NO: 2947)		
1008B10	970	141-248	162-172	188-194	237-237	1-125	26-35	99-114	EGYDLITGLYHLYHGMDF (SEQ ID NO: 2753)		
1008B11	971	144-254	166-179	192-198	231-240	1-128	26-35	99-117	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1008C06	972	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1008C08	973	149-255	171-183	199-205	238-240	1-125	26-35	99-112	GRFGYDLITGLYLSLSADAF (SEQ ID NO: 2729)		
1008C09	974	142-249	163-173	189-195	238-238	1-126	26-35	99-115	ATYDPLIGYSFGDEH (SEQ ID NO: 2973)		
1008D01	975	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1008D02	976	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ENYDNLITGLYAGLDMF (SEQ ID NO: 2751)		
1008D03	977	144-254	166-179	192-198	231-240	1-128	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1008D04	978	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1008D05	979	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1008D06	980	141-248	166-179	188-194	237-237	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		
1008D07	981	144-254	166-179	192-198	231-240	1-128	26-35	99-117	DREYDLITGLYTHHGADF (SEQ ID NO: 2837)		
1008D08	982	144-251	163-175	191-197	230-240	1-128	26-35	99-117	LPYDLITGLYTHYGMDF (SEQ ID NO: 2924)		
1008D12	983	144-254	166-179	192-198	231-240	1-128	26-35	99-117	ATYDPLIGYSFGDEH (SEQ ID NO: 2934)		
1008E01	984	141-248	162-172	188-194	237-237	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2891)		
1008E02	985	137-247	159-172	188-194	237-236	1-121	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2954)		
1008E03	986	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLIGYSFGDEH (SEQ ID NO: 2153)		



TABLE 1—continued

Clone ID	gsFV SEQ ID NO	gsFv that Immunoreactively Bind to BLA5									
		AAs of VL	AAs of VL CDR3	AAs of VL CDR2	AAs of VL CDR1	AAs of VH	AAs of VH CDR3	AAs of VH CDR2	AAs of VH CDR1	AAs of VH CDR3	AAs of VH CDR2
D008E04	987	141-248	162-172	188-194	227-237	1-125	26-35	50-66	98-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	SVNLTGYSDGEDI (SEQ ID NO: 2153)
D008E08	988	141-252	163-171	191-200	230-241	1-125	26-35	50-66	98-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	SVNLTGYSDGEDI (SEQ ID NO: 2153)
D008E09	989	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	FRADYDLTGYSDGEDI (SEQ ID NO: 2153)	FRADYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E12	990	141-251	163-176	192-198	231-240	1-125	26-37	52-67	100-114	FRYDLTGYSDGEDI (SEQ ID NO: 2153)	FRYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E16	991	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	ATYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E07	992	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	ATYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E08	993	141-250	164-174	190-196	231-240	1-125	26-35	50-66	98-116	FRYDLTGYSDGEDI (SEQ ID NO: 2153)	FRYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E09	994	143-253	165-168	184-190	233-242	1-127	26-35	50-66	98-116	FRYDLTGYSDGEDI (SEQ ID NO: 2153)	FRYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E09	995	133-243	155-168	184-190	233-242	1-127	26-35	50-66	98-116	FRYDLTGYSDGEDI (SEQ ID NO: 2153)	FRYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E10	996	140-247	161-171	191-197	226-236	1-124	26-35	50-66	99-113	SVNLTGYSDGEDI (SEQ ID NO: 2153)	SVNLTGYSDGEDI (SEQ ID NO: 2153)
D008E11	997	144-251	165-175	191-197	230-240	1-128	26-35	50-66	101-117	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	ATYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E12	998	144-251	165-175	192-198	231-240	1-125	26-35	50-66	99-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	ATYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E13	999	140-247	163-173	190-196	231-240	1-125	26-35	50-66	99-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	ATYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E04	1000	140-247	165-178	194-200	233-242	1-127	26-35	50-66	99-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	ATYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E05	1001	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-116	FRYDLTGYSDGEDI (SEQ ID NO: 2153)	FRYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E11	1002	136-246	158-171	187-193	226-235	1-120	26-35	50-66	99-116	FRYDLTGYSDGEDI (SEQ ID NO: 2153)	FRYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E12	1003	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	ATYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E13	1004	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	ATYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E14	1005	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	ATYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E15	1006	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	ATYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E16	1007	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	ATYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E17	1008	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	ATYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E18	1009	140-249	163-175	191-197	229-237	1-125	26-35	50-66	99-114	ATYDLTGYSDGEDI (SEQ ID NO: 2153)	ATYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E19	1010	140-249	163-175	192-198	230-239	1-124	26-34	49-65	99-113	ELGSLVGGTALDM (SEQ ID NO: 2174)	ELGSLVGGTALDM (SEQ ID NO: 2174)
D008E20	1011	140-251	164-176	192-198	231-241	1-124	26-34	49-65	99-113	ELGSLVGGTALDM (SEQ ID NO: 2174)	ELGSLVGGTALDM (SEQ ID NO: 2174)
D008E21	1012	142-255	165-178	194-200	233-244	1-128	26-35	50-66	99-116	FRYDLTGYSDGEDI (SEQ ID NO: 2153)	FRYDLTGYSDGEDI (SEQ ID NO: 2153)
D008E22	1013	140-251	164-174	190-196	229-239	1-124	26-34	49-65	99-113	ELGSLVGGTALDM (SEQ ID NO: 2174)	ELGSLVGGTALDM (SEQ ID NO: 2174)
D008E23	1014	140-251	164-174	190-196	229-239	1-124	26-34	49-65	99-113	ELGSLVGGTALDM (SEQ ID NO: 2174)	ELGSLVGGTALDM (SEQ ID NO: 2174)
D008E24	1015	145-256	168-180	196-202	235-245	1-129	26-35	50-66	99-118	DRGNGYDLTGYTHGYSDY (SEQ ID NO: 2174)	DRGNGYDLTGYTHGYSDY (SEQ ID NO: 2174)
D008E25	1016	140-252	164-176	192-198	231-241	1-124	26-34	49-65	99-113	ELGSLVGGTALDM (SEQ ID NO: 2174)	ELGSLVGGTALDM (SEQ ID NO: 2174)
D008E26	1017	140-252	164-176	192-198	231-241	1-124	26-34	49-65	99-113	ELGSLVGGTALDM (SEQ ID NO: 2174)	ELGSLVGGTALDM (SEQ ID NO: 2174)
D008E27	1018	140-249	163-173	189-195	228-238	1-124	26-34	49-65	99-113	ELGSLVGGTALDM (SEQ ID NO: 2174)	ELGSLVGGTALDM (SEQ ID NO: 2174)
D008E28	1019	140-249	163-173	189-195	228-238	1-124	26-34	49-65	99-113	ELGSLVGGTALDM (SEQ ID NO: 2174)	ELGSLVGGTALDM (SEQ ID NO: 2174)
D008E29	1020	140-251	164-176	192-198	231-241	1-124	26-34	49-65	99-113	ELGSLVGGTALDM (SEQ ID NO: 2174)	ELGSLVGGTALDM (SEQ ID NO: 2174)
D008E30	1021	140-252	164-176	192-198	231-241	1-124	26-34	49-65	99-113	ELGSLVGGTALDM (SEQ ID NO: 2174)	ELGSLVGGTALDM (SEQ ID NO: 2174)
D008E31	1022	139-249	163-173	189-195	228-239	1-123	26-35	50-66	99-112	RYGDPFYTYMYNMV (SEQ ID NO: 2755)	RYGDPFYTYMYNMV (SEQ ID NO: 2755)
D008E32	1023	140-251	164-176	192-198	231-241	1-124	26-34	49-65	99-113	ELGSLVGGTALDM (SEQ ID NO: 2174)	ELGSLVGGTALDM (SEQ ID NO: 2174)
D008E33	1024	140-249	163-173	189-195	228-238	1-124	26-34	49-65	99-113	ELGSLVGGTALDM (SEQ ID NO: 2174)	ELGSLVGGTALDM (SEQ ID NO: 2174)
D008E34	1025	147-259	170-182	194-204	237-248	1-131	26-35	50-66	99-120	SPPKVYDLTGYTHGYSDY (SEQ ID NO: 2174)	SPPKVYDLTGYTHGYSDY (SEQ ID NO: 2174)
D008E35	1026	147-256	171-181	194-204	237-245	1-131	26-35	50-66	99-120	SPPKVYDLTGYTHGYSDY (SEQ ID NO: 2174)	SPPKVYDLTGYTHGYSDY (SEQ ID NO: 2174)
D008E36	1027	147-256	171-181	194-204	237-245	1-131	26-35	50-66	99-120	SPPKVYDLTGYTHGYSDY (SEQ ID NO: 2174)	SPPKVYDLTGYTHGYSDY (SEQ ID NO: 2174)
D008E37	1028	147-257	172-182	194-204	237-246	1-131	26-35	50-66	99-120	SPPKVYDLTGYTHGYSDY (SEQ ID NO: 2174)	SPPKVYDLTGYTHGYSDY (SEQ ID NO: 2174)
D008E38	1029	147-257	172-182	194-204	237-246	1-131	26-35	50-66	99-120	SPPKVYDLTGYTHGYSDY (SEQ ID NO: 2174)	SPPKVYDLTGYTHGYSDY (SEQ ID NO: 2174)
D008E39	1030	147-257	172-182	194-204	237-246	1-131	26-35	50-66	99-120	SPPKVYDLTGYTHGYSDY (SEQ ID NO: 2174)	SPPKVYDLTGYTHGYSDY (SEQ ID NO: 2174)
D008E40	1031	137-249	160-173	189-195	228-237	1-121	26-35	50-66	99-110	GYDSSAFRAEDI (SEQ ID NO: 2136)	GYDSSAFRAEDI (SEQ ID NO: 2136)
D008E41	1032	147-259	170-183	194-204	237-248	1-131	26-35	50-66	99-118	GURHYTLGTYGTHGYSDY (SEQ ID NO: 2189)	GURHYTLGTYGTHGYSDY (SEQ ID NO: 2189)
D008E42	1033	145-257	168-181	197-203	236-246	1-129	26-35	50-66	99-118	GURHYTLGTYGTHGYSDY (SEQ ID NO: 2189)	GURHYTLGTYGTHGYSDY (SEQ ID NO: 2189)

TABLE 1-continued

Close ID	ssF <sub>2</sub> SEQ ID NO	ssF <sub>2</sub> that Immunogenically Bind to B1A5									
		AAs of VL	AAs of VL CDR3	AAs of VL CDR2	AAs of VL CDR3	AAs of VL CDR2	AAs of VL CDR3	AAs of VL CDR2	AAs of VL CDR3	AAs of VL CDR2	AAs of VL CDR3
1013E02	1034	147-259	170-183	199-205	238-248	1-131	26-35	50-66	98-120	GRGIDTKVLPWRYTHYYVMDV (SEQ ID NO: 2809)	
1013E05	1035	137-249	160-173	189-205	238-248	1-121	26-35	50-66	98-120	GRGIDTKVLPWRYTHYYVMDV (SEQ ID NO: 2186)	
1013E09	1036	147-260	170-183	199-205	238-249	1-121	26-35	50-66	98-120	SSPKRYDALTGHSSTHSAADV (SEQ ID NO: 2165)	
1013F01	1037	137-248	160-172	188-194	227-237	1-131	26-35	50-66	99-110	GYSSAFRAFDI (SEQ ID NO: 2186)	
1013F04	1038	147-258	170-182	198-204	237-247	1-131	26-35	50-66	99-110	SSPKRYDALTGHSSTHSAADV (SEQ ID NO: 2159)	
1013F07	1039	145-260	170-185	201-207	240-249	1-129	26-35	50-66	99-110	AATSKQNKRYATVYGMVDV (SEQ ID NO: 2131)	
1013F09	1040	137-248	160-172	198-194	237-237	1-131	26-35	50-66	99-110	GYSSAFRAFDI (SEQ ID NO: 2186)	
1013F10	1041	147-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120	SSPKRYDALTGHSSTHSAADV (SEQ ID NO: 2159)	
1013F14	1042	147-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120	SSPKRYDALTGHSSTHSAADV (SEQ ID NO: 2159)	
1013F07	1043	147-259	170-183	199-205	238-248	1-131	26-35	50-66	99-116	GRGIDTKVLPWRYTHYYVMDV (SEQ ID NO: 2809)	
1014X12	1044	147-253	165-178	194-200	233-242	1-125	26-35	50-66	99-114	EGGYDLITGVYNGAGFDI (SEQ ID NO: 2158)	
1016A08	1045	141-254	164-177	193-200	233-243	1-125	26-35	50-66	99-114	GYDYLITGVPAECTQI (SEQ ID NO: 2884)	
1016A10	1046	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1014C10	1047	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1014C12	1048	140-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGHSYDALTGALDM (SEQ ID NO: 2174)	
1014E06	1049	141-251	166-176	192-198	231-240	1-125	26-37	52-67	100-114	AYDYLITGVTPDS (SEQ ID NO: 2757)	
1014F02	1050	141-251	166-176	192-198	231-240	1-128	26-35	50-66	99-117	EVNTDLITGVYLAGPLDI (SEQ ID NO: 2751)	
1016A08	1051	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1016A10	1052	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1016C03	1053	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1016C05	1054	148-255	169-179	195-201	234-244	1-132	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1016C09	1055	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-121	VQMDSEYDILITGVNVPYVDY (SEQ ID NO: 2132)	
1016C11	1056	148-255	169-179	195-201	234-244	1-132	26-35	50-66	99-121	VQMDSEYDILITGVNVPYVDY (SEQ ID NO: 2132)	
1016C13	1057	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1016D11	1058	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1016E03	1059	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1016E04	1060	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1016E05	1061	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1016F11	1062	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1016F13	1063	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1016F15	1064	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1016G12	1065	148-255	169-179	195-201	234-244	1-132	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1016H10	1066	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1017A06	1067	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1017A07	1068	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1017A11	1069	140-253	162-175	191-197	233-242	1-124	25-34	49-65	98-113	VQMDSEYDILITGVNVPYVDY (SEQ ID NO: 2133)	
1017B11	1070	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1017G03	1071	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1017G07	1072	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1017H01	1073	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1018A02	1074	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1018A04	1075	144-251	166-179	196-201	234-243	1-128	26-35	50-66	99-117	EGSYDILITGVYNGAGVDV (SEQ ID NO: 2171)	
1018A06	1076	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1018A11	1077	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1018B02	1078	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1018B08	1079	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	
1018C04	1080	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLITGVSEDFGDI (SEQ ID NO: 2153)	

TABLE 1-continued

Conte ID	scFv SEQ ID NO	scFvs that Immunogenetically Bind to B15.5									
		AAs of VL	AAs of VH	AAs of VL CDR3	AAs of VH CDR3	AAs of VL CDR1	AAs of VH CDR2	AAs of VH CDR3	Sequence (SEQ ID NO)		
1018D02	1081	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDLPLGYSGDGH (SEQ ID NO: 2153)		
1018E06	1082	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDLPLGYSGDGH (SEQ ID NO: 2153)		
1018E08	1083	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDLPLGYSGDGH (SEQ ID NO: 2153)		
1018F04	1084	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDLPLGYSGDGH (SEQ ID NO: 2153)		
1018F06	1085	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDLPLGYSGDGH (SEQ ID NO: 2153)		
1018G07	1086	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDLPLGYSGDGH (SEQ ID NO: 2153)		
1018H07	1087	144-254	166-179	195-201	234-243	1-128	26-35	99-117	EHYVDLITGYGMDY (SEQ ID NO: 2784)		
1019F06	1088	144-254	166-179	195-201	234-243	1-128	26-35	99-117	EHYVDLITGYGMDY (SEQ ID NO: 2784)		
1019G12	1089	143-253	165-178	194-200	233-242	1-127	24-33	97-116	EGGNYDLITGYGNGAFH (SEQ ID NO: 2158)		
1020D01	1090	137-247	159-171	187-193	226-236	1-121	26-35	99-110	DRETKVGYGMDY (SEQ ID NO: 2845)		
1020G05	1091	143-253	165-178	194-200	233-242	1-127	24-33	97-116	EGGNYDLITGYGNGAFH (SEQ ID NO: 2158)		
1020H06	1092	143-253	165-178	194-200	233-242	1-127	24-33	97-116	EGGNYDLITGYGNGAFH (SEQ ID NO: 2158)		
1020H06	1093	143-253	165-178	194-200	233-242	1-127	24-33	97-116	EGGNYDLITGYGNGAFH (SEQ ID NO: 2158)		
1020H06	1094	143-253	165-178	194-200	233-242	1-127	24-33	97-116	EGGNYDLITGYGNGAFH (SEQ ID NO: 2158)		
1020H11	1095	143-253	165-178	194-200	233-242	1-127	24-33	97-116	EGGNYDLITGYGNGAFH (SEQ ID NO: 2158)		
1021A01	1096	143-253	165-178	194-200	233-242	1-127	24-33	97-116	EGGNYDLITGYGNGAFH (SEQ ID NO: 2158)		
1021B01	1097	143-253	165-178	194-200	233-242	1-127	24-33	97-116	EGGNYDLITGYGNGAFH (SEQ ID NO: 2158)		
1021B01	1098	143-253	165-178	194-200	233-242	1-127	24-33	97-116	EGGNYDLITGYGNGAFH (SEQ ID NO: 2158)		
1021D12	1099	137-247	159-171	187-193	226-236	1-121	26-35	99-110	DRETKVGYGMDY (SEQ ID NO: 2845)		
1021E10	1100	143-253	165-178	194-200	233-242	1-127	24-33	97-116	EGGNYDLITGYGNGAFH (SEQ ID NO: 2158)		
1021G02	1101	143-253	165-178	194-200	233-242	1-127	24-33	97-116	EGGNYDLITGYGNGAFH (SEQ ID NO: 2158)		
1022A08	1102	142-249	163-173	189-195	228-238	1-126	26-35	99-115	ATYDLPLGYSGDGH (SEQ ID NO: 2153)		
1022B01	1103	141-251	163-176	192-198	231-240	1-125	26-35	99-114	MEYDLITGYGVDY (SEQ ID NO: 2179)		
1022B01	1104	141-248	164-174	190-196	229-237	1-125	26-35	99-115	MEYDLITGYGVDY (SEQ ID NO: 2179)		
1022C04	1105	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDLPLGYSGDGH (SEQ ID NO: 2153)		
1022C04	1106	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDLPLGYSGDGH (SEQ ID NO: 2153)		
1022C08	1107	141-251	163-176	192-198	231-240	1-125	26-35	99-115	ASYDLITGYGKAFH (SEQ ID NO: 2155)		
1022D06	1108	142-249	163-173	189-195	228-238	1-126	26-35	99-115	ASYDLITGYGKAFH (SEQ ID NO: 2155)		
1022F08	1109	142-249	163-173	189-195	228-238	1-126	26-35	99-115	ASYDLITGYGKAFH (SEQ ID NO: 2155)		
1022F08	1110	142-249	163-173	189-195	228-238	1-126	26-35	99-115	ASYDLITGYGKAFH (SEQ ID NO: 2155)		
1022F08	1111	142-249	163-173	189-195	228-238	1-126	26-35	99-115	ASYDLITGYGKAFH (SEQ ID NO: 2155)		
1022F12	1112	140-247	161-171	187-193	226-236	1-126	26-35	99-114	SPYDLITGNYLFFY (SEQ ID NO: 2166)		
1022G11	1113	142-249	163-173	189-195	228-238	1-126	26-35	99-115	ASYDLITGYGKAFH (SEQ ID NO: 2155)		
1023G11	1114	141-251	163-176	192-198	231-240	1-125	26-35	99-115	ASYDLITGYGKAFH (SEQ ID NO: 2155)		
1023P04	1115	142-249	163-173	189-195	228-238	1-126	26-35	99-115	ASYDLITGYGKAFH (SEQ ID NO: 2155)		
1023P04	1116	140-247	161-171	187-193	226-236	1-126	26-35	99-113	GVYDLITGYGMDY (SEQ ID NO: 2155)		
1023P04	1117	140-247	161-171	187-193	226-236	1-126	26-35	99-113	GVYDLITGYGMDY (SEQ ID NO: 2155)		
1023P04	1118	142-249	163-173	189-195	228-238	1-126	26-35	99-115	GVYDLITGYGMDY (SEQ ID NO: 2155)		
1023P04	1119	142-249	163-173	189-195	228-238	1-126	26-35	99-115	GVYDLITGYGMDY (SEQ ID NO: 2155)		
1023P04	1120	142-249	163-173	189-195	228-238	1-126	26-35	99-115	GVYDLITGYGMDY (SEQ ID NO: 2155)		
1023A01	1121	140-251	163-176	191-197	230-240	1-124	26-34	99-113	ELGSLVATGATGDM (SEQ ID NO: 2174)		
1023A04	1122	140-251	163-176	191-197	230-240	1-124	26-34	99-113	ELGSLVATGATGDM (SEQ ID NO: 2174)		
1023A04	1123	140-251	163-176	191-197	230-240	1-124	26-34	99-113	ELGSLVATGATGDM (SEQ ID NO: 2174)		
1023B01	1124	137-247	159-171	187-193	226-236	1-121	26-35	99-110	DRETKVGYGMDY (SEQ ID NO: 2845)		
1023B01	1125	140-254	166-176	192-198	233-243	1-127	26-35	99-113	ELGSLVATGATGDM (SEQ ID NO: 2174)		
1023B01	1126	140-251	163-176	192-198	233-243	1-127	26-35	99-113	ELGSLVATGATGDM (SEQ ID NO: 2174)		
1023C07	1127	140-251	163-176	192-198	231-240	1-124	26-34	99-113	ELGSLVATGATGDM (SEQ ID NO: 2852)		

TABLE 1-continued

Clone ID	sFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VH	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
102SD11	1128	140-252	164-176	231-241	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE04	1129	142-252	164-176	231-241	1-26	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE05	1130	140-251	163-175	230-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE07	1131	140-252	164-176	231-241	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE08	1132	139-251	163-175	229-239	1-23	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE09	1133	139-251	163-175	229-239	1-23	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE10	1134	137-248	160-172	227-237	1-21	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE11	1135	140-252	164-176	231-241	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE12	1136	140-254	163-176	231-243	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE13	1137	144-255	167-179	234-244	1-28	26-35	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE14	1138	141-249	164-176	231-240	1-23	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE15	1139	140-251	163-175	230-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE16	1140	140-251	163-175	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE17	1141	140-251	163-175	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE18	1142	138-249	161-174	229-238	1-22	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE19	1143	141-251	163-176	231-240	1-23	26-35	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE20	1144	139-252	162-175	230-241	1-23	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE21	1145	140-251	163-175	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE22	1146	140-251	163-175	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE23	1147	140-251	163-176	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE24	1148	140-251	163-176	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE25	1149	140-251	163-176	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE26	1150	140-256	163-176	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE27	1151	140-251	163-176	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE28	1152	140-251	163-176	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE29	1153	143-255	166-179	234-244	1-28	26-35	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE30	1154	139-251	162-175	230-240	1-23	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE31	1155	140-251	163-175	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE32	1156	144-255	167-179	234-244	1-28	26-35	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE33	1157	140-251	163-176	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE34	1158	139-250	161-174	229-239	1-22	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE35	1159	140-250	161-174	229-239	1-22	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE36	1160	138-249	161-174	229-239	1-22	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE37	1161	141-250	164-174	230-239	1-23	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE38	1162	140-251	163-176	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE39	1163	140-252	164-176	231-241	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE40	1164	140-252	164-176	231-241	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE41	1165	140-254	163-176	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE42	1166	140-253	163-176	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE43	1167	140-253	163-176	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE44	1168	140-250	164-174	229-239	1-22	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE45	1169	141-252	164-176	231-241	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE46	1170	140-251	163-175	230-240	1-23	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE47	1171	141-251	163-176	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE48	1172	141-251	163-176	231-240	1-24	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE49	1173	148-258	170-183	238-247	1-13	26-37	ELGSLVATGALDM (SEQ ID NO: 2174)
102SE50	1174	142-250	165-175	230-239	1-23	26-34	ELGSLVATGALDM (SEQ ID NO: 2174)

TABLE 1-continued  
seq: the that Immunoprecipitated to B10.5

Clone ID	seq: SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	seq: the that Immunoprecipitated to B10.5
1028C04	1175	143-253	163-176	194-200	233-242	1-127	26-35	50-66	99-116	DASYDILTYGYTGLAFDM (SEQ ID NO: 2880)
1028C08	1176	141-251	163-176	192-198	231-241	1-125	26-35	50-66	99-114	DASYDILTYGYTGLAFDM (SEQ ID NO: 2881)
1028D04	1177	140-247	163-173	189-195	228-236	1-124	26-35	50-66	99-114	ATDGLITGLYSGMDV (SEQ ID NO: 2882)
1028D08	1178	141-248	163-174	188-194	227-237	1-125	26-35	50-66	99-113	HYDILTYGYLLGMDV (SEQ ID NO: 2883)
1028D12	1179	141-248	163-174	190-196	229-239	1-127	26-35	50-66	99-116	EGSYDILTYGYVGMADV (SEQ ID NO: 2884)
1028E06	1180	143-253	166-178	196-202	233-242	1-127	26-35	50-66	99-116	EGSYDILTYGYVGMADV (SEQ ID NO: 2885)
1028E07	1181	141-248	163-172	188-194	227-237	1-125	26-35	50-66	99-114	ATDPLTYGSDGHD (SEQ ID NO: 2886)
1028E08	1182	141-248	163-172	188-194	227-237	1-125	26-35	50-66	99-114	ATDPLTYGSDGHD (SEQ ID NO: 2887)
1028E09	1183	146-256	168-180	196-202	233-245	1-130	26-35	50-66	99-119	DDRGYDILTYGYTGLAFDM (SEQ ID NO: 2888)
1028F08	1184	134-244	156-169	185-191	234-233	1-118	26-35	50-66	99-107	DYGSGVGSSTDMGV (SEQ ID NO: 2889)
1028F09	1185	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-117	EVNYDILTYGYTGLAFDM (SEQ ID NO: 2890)
1028G08	1186	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATDPLTYGSDGHD (SEQ ID NO: 2891)
1028G10	1187	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATDPLTYGSDGHD (SEQ ID NO: 2892)
1028H02	1188	142-249	165-175	191-197	230-238	1-126	26-37	50-66	99-121	SPSYDILTYGYTGLAFDM (SEQ ID NO: 2893)
1028H03	1189	148-256	169-179	195-201	234-244	1-129	26-35	50-66	99-118	DDPSYDILTYGYTGLAFDM (SEQ ID NO: 2894)
1028H06	1190	145-255	167-180	196-202	235-244	1-129	26-35	50-66	101-113	EDDILTYGYTGLAFDM (SEQ ID NO: 2895)
1028H09	1191	140-250	162-175	191-197	230-239	1-124	26-35	50-66	101-110	RDILTYGYTGLAFDM (SEQ ID NO: 2896)
1028H10	1192	140-250	162-175	191-197	230-239	1-124	26-35	50-66	101-110	RDILTYGYTGLAFDM (SEQ ID NO: 2897)
1028H12	1193	137-247	159-171	188-193	228-235	1-125	26-35	50-66	99-117	EVNYDILTYGYTGLAFDM (SEQ ID NO: 2898)
1028H13	1194	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-117	EVNYDILTYGYTGLAFDM (SEQ ID NO: 2899)
1028H14	1195	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVNYDILTYGYTGLAFDM (SEQ ID NO: 2900)
1028H15	1196	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVNYDILTYGYTGLAFDM (SEQ ID NO: 2901)
1028H16	1197	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVNYDILTYGYTGLAFDM (SEQ ID NO: 2902)
1028H17	1198	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVNYDILTYGYTGLAFDM (SEQ ID NO: 2903)
1028H18	1199	142-253	165-177	191-197	227-237	1-125	26-35	50-66	99-114	GYVDILTYGYTGLAFDM (SEQ ID NO: 2904)
1028H19	1200	140-253	165-177	191-197	227-237	1-125	26-35	50-66	99-114	GYVDILTYGYTGLAFDM (SEQ ID NO: 2905)
1028H20	1201	140-253	165-177	191-197	227-237	1-125	26-35	50-66	99-114	GYVDILTYGYTGLAFDM (SEQ ID NO: 2906)
1028H21	1202	140-253	165-177	191-197	227-237	1-125	26-35	50-66	99-114	GYVDILTYGYTGLAFDM (SEQ ID NO: 2907)
1028H22	1203	140-253	165-177	191-197	227-237	1-125	26-35	50-66	99-114	GYVDILTYGYTGLAFDM (SEQ ID NO: 2908)
1028H23	1204	140-253	165-177	191-197	227-237	1-125	26-35	50-66	99-114	GYVDILTYGYTGLAFDM (SEQ ID NO: 2909)
1028H24	1205	139-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112	RYGDPLTYGYTGLAFDM (SEQ ID NO: 2910)
1028H25	1206	140-253	165-177	191-197	227-237	1-125	26-35	50-66	99-112	RYGDPLTYGYTGLAFDM (SEQ ID NO: 2911)
1028H26	1207	141-251	163-176	192-198	231-241	1-124	26-34	49-65	99-113	ELGSLVGTGLAFDM (SEQ ID NO: 2912)
1028H27	1208	139-252	162-175	191-197	228-238	1-123	26-35	50-66	99-112	ELGSLVGTGLAFDM (SEQ ID NO: 2913)
1028H28	1209	146-256	169-182	198-204	237-245	1-130	26-35	50-66	99-112	ELGSLVGTGLAFDM (SEQ ID NO: 2914)
1028H29	1210	146-256	169-182	198-204	237-245	1-130	26-35	50-66	99-112	ELGSLVGTGLAFDM (SEQ ID NO: 2915)
1028H30	1211	140-253	165-177	191-197	227-237	1-125	26-35	50-66	99-113	ELGSLVGTGLAFDM (SEQ ID NO: 2916)
1028H31	1212	140-253	165-177	191-197	227-237	1-125	26-35	50-66	99-113	ELGSLVGTGLAFDM (SEQ ID NO: 2917)
1028H32	1213	139-251	162-175	191-197	228-238	1-123	26-35	50-66	99-112	RYGDPLTYGYTGLAFDM (SEQ ID NO: 2918)
1028H33	1214	139-251	162-175	191-197	228-238	1-123	26-35	50-66	99-112	RYGDPLTYGYTGLAFDM (SEQ ID NO: 2919)
1028H34	1215	139-249	163-173	189-195	226-236	1-123	26-35	50-66	99-112	RYGDPLTYGYTGLAFDM (SEQ ID NO: 2920)
1028H35	1216	140-251	163-175	191-197	229-240	1-123	26-35	50-66	99-112	RYGDPLTYGYTGLAFDM (SEQ ID NO: 2921)
1028H36	1217	140-251	163-175	191-197	229-240	1-123	26-35	50-66	99-112	RYGDPLTYGYTGLAFDM (SEQ ID NO: 2922)
1028H37	1218	140-251	163-175	191-197	229-240	1-123	26-35	50-66	99-112	RYGDPLTYGYTGLAFDM (SEQ ID NO: 2923)
1028H38	1219	140-251	163-175	191-197	229-240	1-123	26-35	50-66	99-112	RYGDPLTYGYTGLAFDM (SEQ ID NO: 2924)
1028H39	1220	140-251	163-175	191-197	229-240	1-123	26-35	50-66	99-112	RYGDPLTYGYTGLAFDM (SEQ ID NO: 2925)
1028H40	1221	140-251	163-175	191-197	229-240	1-123	26-35	50-66	99-112	RYGDPLTYGYTGLAFDM (SEQ ID NO: 2926)
1028H41	1222	140-251	163-175	191-197	229-240	1-123	26-35	50-66	99-112	RYGDPLTYGYTGLAFDM (SEQ ID NO: 2927)

TABLE 1—continued

Clone ID	sFv SEQ ID NO	AA# of VL	AA# of VL CDR2	AA# of VL CDR3	AA# of VH	AA# of VH CDR2	AA# of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
03I0E10	1221	139-250	160-174	190-196	229-239	1-123	99-112	RYGPFYFYFYFYFY (SEQ ID NO: 2755)
03I0E02	1222	164-176	161-175	191-197	231-241	1-125	100-113	RYGPFYFYFYFYFY (SEQ ID NO: 2757)
03I0E05	1223	140-251	163-175	191-197	230-240	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0E06	1224	139-251	163-175	191-197	230-240	1-124	99-112	RYGPFYFYFYFYFY (SEQ ID NO: 2755)
03I0E07	1225	163-175	163-175	191-197	231-241	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0E09	1226	140-251	163-175	191-197	230-240	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0E11	1227	139-250	160-174	190-196	229-239	1-123	99-112	RYGPFYFYFYFYFY (SEQ ID NO: 2755)
03I0E12	1228	140-251	163-175	191-197	230-240	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0E13	1229	140-251	163-175	191-197	230-240	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0E14	1230	140-251	163-175	191-197	230-240	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0E15	1231	139-251	163-175	191-197	230-240	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0E16	1232	140-251	163-175	191-197	230-240	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0E17	1233	140-251	163-175	191-197	230-240	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0E18	1234	146-258	170-182	198-204	231-241	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0E19	1235	140-251	163-175	191-197	230-240	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0E20	1236	140-251	163-175	191-197	230-240	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0E21	1237	137-248	160-175	192-198	231-241	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0A01	1238	141-251	166-176	192-198	231-241	1-125	102-119	ATKSYDILIRYTHYHMDV (SEQ ID NO: 2748)
03I0A02	1239	141-251	166-176	192-198	231-241	1-125	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0A03	1240	146-257	168-182	198-204	231-241	1-124	98-113	ELGYSVATGALD (SEQ ID NO: 2758)
03I0A04	1241	136-246	159-172	188-194	227-237	1-126	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0B06	1242	142-253	165-177	193-199	232-242	1-125	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0B07	1243	147-258	170-182	199-205	237-247	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0B08	1244	147-258	170-182	199-205	237-247	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0B09	1245	147-258	170-182	199-205	237-247	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0B10	1246	137-248	160-172	193-199	232-242	1-125	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0B11	1247	147-259	170-183	199-205	237-247	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0B12	1248	137-248	160-172	193-199	232-242	1-125	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0C01	1249	141-253	164-177	193-199	232-242	1-125	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0C02	1250	147-260	171-183	199-205	238-248	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0C03	1251	147-260	171-183	199-205	238-248	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0C04	1252	147-260	171-183	199-205	238-248	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0C05	1253	147-260	171-183	199-205	238-248	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0D01	1254	145-256	168-180	196-202	235-245	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0D02	1255	137-248	160-172	193-199	232-242	1-125	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0D03	1256	147-258	170-182	198-204	237-247	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0D04	1257	144-257	167-180	196-202	235-245	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0D05	1258	147-259	170-183	199-205	238-248	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0D06	1259	144-254	168-178	194-200	237-247	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0D07	1260	147-258	170-182	198-204	237-247	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0E01	1261	147-257	171-181	197-203	236-246	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0E02	1262	147-259	170-182	199-205	238-248	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0E03	1263	147-259	170-182	199-205	238-248	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0E04	1264	147-259	170-182	199-205	238-248	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0E05	1265	147-258	170-182	198-204	237-247	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0E06	1266	147-258	170-182	198-204	237-247	1-131	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0E07	1267	137-246	160-172	188-194	227-237	1-121	99-110	GYSSAFAD (SEQ ID NO: 2744)
03I0E08	1268	137-246	160-172	188-194	227-237	1-121	99-110	GYSSAFAD (SEQ ID NO: 2744)

TABLE 1-continued

Clone ID	gpV SEQ ID NO	sFv that Immunogenically Bind to BLAS									
		AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	AAs of VH CDR3	AAs of VH CDR3	AAs of VH CDR3
1031F06	1269	135-247	159-171	187-193	226-236	1-131	26-35	50-66	98-108	DRYDLSGMDV (SEQ ID NO: 2804)	
1031F10	1270	147-259	170-183	199-203	238-246	1-131	26-35	50-66	99-120	GRDIDTKYKPKWRKYHYHYMDV (SEQ ID NO: 2809)	
1031F11	1271	144-255	167-179	195-201	234-244	1-128	26-35	50-66	99-117	DKAHGEGRDYHYHYMDV (SEQ ID NO: 2755)	
1031G01	1272	137-249	160-172	188-194	227-237	1-121	26-35	50-66	99-110	DYSSSARAFTI (SEQ ID NO: 2136)	
1031G03	1274	147-258	170-182	199-203	237-247	1-131	26-35	50-66	99-120	SSPKWYDALGHSHVHSAEMV (SEQ ID NO: 2159)	
1031G05	1275	147-259	170-183	199-203	238-248	1-131	26-35	50-66	99-120	GRDIDTKYKPKWRKYHYHYMDV (SEQ ID NO: 2809)	
1031G06	1276	147-259	170-183	199-203	237-247	1-131	26-35	50-66	99-120	SSPKWYDALGHSHVHSAEMV (SEQ ID NO: 2159)	
1031G09	1278	147-259	171-183	199-202	244-252	1-131	26-35	50-66	99-118	AATYSQRNKYATYFGMDV (SEQ ID NO: 2869)	
1031G12	1279	145-256	168-180	196-200	235-245	1-129	26-35	50-66	99-118	AKGYDSSGASDVPV (SEQ ID NO: 2871)	
1031H01	1280	137-250	160-173	189-195	228-239	1-121	26-35	50-66	99-115	GRDIDTKYKPKWRKYHYHYMDV (SEQ ID NO: 2809)	
1031H02	1281	142-255	165-178	194-200	233-244	1-126	26-35	50-66	99-120	GRDIDTKYKPKWRKYHYHYMDV (SEQ ID NO: 2809)	
1031H03	1282	147-260	170-183	195-205	238-249	1-131	26-35	50-66	99-117	DKAHGEGRDYHYHYMDV (SEQ ID NO: 2755)	
1031H06	1283	144-257	167-179	195-201	234-246	1-128	26-35	50-66	99-117	DKAHGEGRDYHYHYMDV (SEQ ID NO: 2755)	
1031H09	1284	144-256	167-179	195-201	234-244	1-128	26-35	50-66	99-116	DRYDLSGMDV (SEQ ID NO: 2804)	
1031H10	1285	143-256	166-179	196-192	225-235	1-127	26-35	50-66	99-108	DRYDLSGMDV (SEQ ID NO: 2804)	
1031H11	1286	135-246	158-170	186-192	221-231	1-123	26-37	52-69	102-117	GRDIDTKYKPKWRKYHYHYMDV (SEQ ID NO: 2809)	
1031H11	1287	144-254	166-179	195-201	234-243	1-128	26-37	52-69	102-117	GRDIDTKYKPKWRKYHYHYMDV (SEQ ID NO: 2809)	
1031H11	1288	144-254	166-179	195-201	234-243	1-128	26-37	52-69	102-117	GRDIDTKYKPKWRKYHYHYMDV (SEQ ID NO: 2809)	
1031H11	1289	144-254	166-179	195-201	234-243	1-128	26-37	52-69	102-117	GRDIDTKYKPKWRKYHYHYMDV (SEQ ID NO: 2809)	
1031H11	1290	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-117	GRDIDTKYKPKWRKYHYHYMDV (SEQ ID NO: 2809)	
1031H11	1291	138-245	161-173	187-193	226-234	1-122	26-35	50-66	99-114	ATYDPLGYSDEGDI (SEQ ID NO: 2153)	
1031H11	1292	141-251	163-176	192-198	232-242	1-127	26-35	50-66	99-114	ATYDPLGYSDEGDI (SEQ ID NO: 2153)	
1031H11	1293	141-251	163-176	192-198	232-242	1-127	26-35	50-66	99-114	ATYDPLGYSDEGDI (SEQ ID NO: 2153)	
1031H11	1294	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	KRADLGYVEGMDV (SEQ ID NO: 2869)	
1031H11	1295	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-112	DYSSSARAFTI (SEQ ID NO: 2136)	
1031H11	1296	139-249	161-173	189-195	228-238	1-123	26-35	50-66	99-114	ATYDPLGYSDEGDI (SEQ ID NO: 2153)	
1031H11	1297	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLGYSDEGDI (SEQ ID NO: 2153)	
1031H11	1298	142-249	161-173	191-199	232-242	1-127	26-35	50-66	99-116	HRSSCSSTSCNDADI (SEQ ID NO: 2770)	
1031H11	1299	142-249	161-173	191-199	232-242	1-127	26-35	50-66	99-116	HRSSCSSTSCNDADI (SEQ ID NO: 2770)	
1031H11	1300	142-249	161-173	191-199	232-242	1-127	26-35	50-66	99-116	HRSSCSSTSCNDADI (SEQ ID NO: 2770)	
1031H11	1301	145-256	167-179	195-201	234-243	1-128	26-35	50-66	99-115	EMGYDILGYLYNMDV (SEQ ID NO: 2862)	
1031H11	1302	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EGYDILGYLYNMDV (SEQ ID NO: 2767)	
1031H11	1303	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EGYDILGYLYNMDV (SEQ ID NO: 2767)	
1031H11	1304	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EGYDILGYLYNMDV (SEQ ID NO: 2767)	
1031H11	1305	142-249	161-173	189-195	228-238	1-126	26-35	50-66	99-115	EMGYDILGYLYNMDV (SEQ ID NO: 2862)	
1031H11	1306	142-249	161-173	189-195	228-238	1-126	26-35	50-66	99-115	EMGYDILGYLYNMDV (SEQ ID NO: 2862)	
1031H11	1307	141-248	160-170	186-192	225-235	1-123	26-35	50-66	99-112	DYSSSARAFTI (SEQ ID NO: 2136)	
1031H11	1308	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-114	ATYDPLGYSDEGDI (SEQ ID NO: 2153)	
1031H11	1309	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112	DYSSSARAFTI (SEQ ID NO: 2136)	
1031H11	1310	141-251	163-175	191-197	232-240	1-125	26-35	50-66	99-114	ATYDPLGYSDEGDI (SEQ ID NO: 2153)	
1031H11	1311	141-251	163-175	191-197	232-240	1-125	26-35	50-66	99-114	ATYDPLGYSDEGDI (SEQ ID NO: 2153)	
1031H11	1312	141-251	163-175	191-197	232-240	1-125	26-35	50-66	99-114	ATYDPLGYSDEGDI (SEQ ID NO: 2153)	
1031H11	1313	141-249	163-173	189-195	232-239	1-124	26-35	50-66	99-115	EMGYDILGYLYNMDV (SEQ ID NO: 2862)	
1031H11	1314	140-250	162-175	191-197	232-239	1-124	26-35	50-66	99-115	EMGYDILGYLYNMDV (SEQ ID NO: 2862)	
1031H11	1315	144-251	163-175	191-197	232-240	1-128	26-35	50-66	99-109	DRYDLSGMDV (SEQ ID NO: 2804)	
1031H11	1316	144-251	163-175	191-197	232-240	1-128	26-35	50-66	99-117	GRDIDTKYKPKWRKYHYHYMDV (SEQ ID NO: 2809)	

TABLE 1 - continued

Conte ID	Seq ID NO	Seqs that Immunogenically Bind to B15.5									
		AAs of VL	AAs of VL CD81	AAs of VL CD82	AAs of VL CD83	AAs of VL CD84	AAs of VL CD85	AAs of VL CD86	AAs of VL CD87	AAs of VL CD88	
037G04	1316	144-251	230-240	1-197	26-35	50-65	98-117	KQGDYDILTYGVGLAFDI (SEQ ID NO: 2808)			
037G05	1317	141-251	231-240	1-98	26-35	50-66	98-117	SHYDILTYGVGLAFDI (SEQ ID NO: 2809)			
037G06	1318	146-256	236-245	1-96	26-35	50-66	99-119	SHYDILTYGVGLAFDI (SEQ ID NO: 2810)			
037G07	1319	140-250	232-240	1-97	26-35	50-66	99-119	DYDILTYGVGLAFDI (SEQ ID NO: 2811)			
042A07	1320	144-251	232-240	1-199	26-35	50-66	99-117	VPSYDILTYGVGLAFDI (SEQ ID NO: 2849)			
042A08	1321	142-249	230-238	1-197	26-35	50-66	98-115	GPYDILTYGVGLAFDI (SEQ ID NO: 2801)			
042B01	1322	140-247	226-236	1-181	26-35	50-66	99-113	DIIDILTYGVGLAFDI (SEQ ID NO: 2824)			
042B02	1323	141-248	227-237	1-182	26-35	50-66	99-114	SHYDILTYGVGLAFDI (SEQ ID NO: 2166)			
042D01	1324	136-246	226-235	1-193	26-35	50-68	99-109	SHYDILTYGVGLAFDI (SEQ ID NO: 2859)			
042D02	1325	140-250	230-239	1-187	26-35	50-68	101-113	SHYDILTYGVGLAFDI (SEQ ID NO: 2859)			
042D03	1326	142-252	227-236	1-193	26-35	50-65	98-115	ERADYDILTYGVGLAFDI (SEQ ID NO: 2802)			
042D04	1327	147-257	227-236	1-204	26-35	50-66	102-120	ERYDILTYGVGLAFDI (SEQ ID NO: 2798)			
042E01	1328	146-256	232-241	1-187	26-35	50-66	99-113	DEYDILTYGVGLAFDI (SEQ ID NO: 2883)			
042F08	1329	142-252	222-241	1-199	26-37	52-67	100-115	GDYDILTYGVGLAFDI (SEQ ID NO: 2738)			
042F12	1330	140-247	222-241	1-187	26-35	50-66	99-113	SHYDILTYGVGLAFDI (SEQ ID NO: 2796)			
042G08	1331	141-248	227-237	1-192	26-35	50-66	99-114	SHYDILTYGVGLAFDI (SEQ ID NO: 2796)			
043G10	1332	141-251	227-237	1-198	26-35	50-65	98-116	GSYDILTYGVGLAFDI (SEQ ID NO: 2759)			
043H01	1333	143-253	228-238	1-205	26-35	50-66	99-117	DGYDILTYGVGLAFDI (SEQ ID NO: 2849)			
043H02	1334	142-249	228-238	1-193	26-35	50-66	98-115	GYDILTYGVGLAFDI (SEQ ID NO: 2744)			
043H03	1335	142-249	228-238	1-195	26-35	50-66	99-116	GYDILTYGVGLAFDI (SEQ ID NO: 2153)			
043H06	1337	143-253	223-242	1-202	26-35	50-66	99-116	ATYDILTYGVGLAFDI (SEQ ID NO: 2153)			
043H07	1338	141-251	223-242	1-194	26-35	50-66	98-116	HYDILTYGVGLAFDI (SEQ ID NO: 2153)			
043H09	1339	143-253	223-242	1-204	26-35	50-65	99-116	TESYDILTYGVGLAFDI (SEQ ID NO: 2727)			
043H10	1340	142-252	224-243	1-205	26-35	50-66	99-117	TESYDILTYGVGLAFDI (SEQ ID NO: 2751)			
043H11	1341	144-250	224-243	1-206	26-35	50-66	99-116	TESYDILTYGVGLAFDI (SEQ ID NO: 2940)			
043H12	1342	141-251	224-243	1-198	26-35	50-66	98-114	ATYDILTYGVGLAFDI (SEQ ID NO: 2153)			
043H13	1343	141-251	224-243	1-198	26-35	50-66	99-114	TESYDILTYGVGLAFDI (SEQ ID NO: 2153)			
043H14	1344	141-251	224-243	1-198	26-35	50-66	99-114	ATYDILTYGVGLAFDI (SEQ ID NO: 2153)			
043H15	1345	143-250	229-239	1-206	26-35	50-66	99-114	ATYDILTYGVGLAFDI (SEQ ID NO: 2153)			
043H16	1346	141-251	229-239	1-192	26-35	50-66	101-117	QGYDILTYGVGLAFDI (SEQ ID NO: 2726)			
043H17	1347	139-249	229-239	1-197	26-35	50-68	99-112	QGYDILTYGVGLAFDI (SEQ ID NO: 2726)			
043H18	1348	140-250	228-238	1-196	26-35	50-66	99-113	QGYDILTYGVGLAFDI (SEQ ID NO: 2726)			
044C10	1349	143-253	228-239	1-206	26-35	50-66	99-116	DKYDILTYGVGLAFDI (SEQ ID NO: 2889)			
044C13	1350	144-254	229-239	1-207	26-35	50-66	99-114	ATYDILTYGVGLAFDI (SEQ ID NO: 2153)			
044D09	1351	141-251	229-239	1-198	26-35	50-66	99-110	AGSLTYGVGLAFDI (SEQ ID NO: 2825)			
044E01	1352	137-247	227-236	1-194	26-35	50-66	99-110	SDYDILTYGVGLAFDI (SEQ ID NO: 2758)			
044E02	1353	143-247	227-236	1-198	26-35	50-66	99-120	DGSLTYGVGLAFDI (SEQ ID NO: 2153)			
044E03	1354	147-257	227-236	1-204	26-35	50-66	99-122	DKYDILTYGVGLAFDI (SEQ ID NO: 2889)			
044E04	1355	141-251	227-236	1-198	26-35	50-66	99-114	SDYDILTYGVGLAFDI (SEQ ID NO: 2758)			
044E05	1356	149-259	228-248	1-206	26-35	50-66	99-117	EVNHYDILTYGVGLAFDI (SEQ ID NO: 2845)			
044H01	1357	144-251	228-248	1-200	26-35	50-66	99-114	DMYDILTYGVGLAFDI (SEQ ID NO: 2846)			
044H02	1358	141-253	228-248	1-191	26-35	50-66	99-114	DYDILTYGVGLAFDI (SEQ ID NO: 2829)			
044H03	1359	141-253	228-248	1-193	26-35	50-66	98-113	DHYDILTYGVGLAFDI (SEQ ID NO: 2728)			
044H04	1360	144-254	232-247	1-219	26-35	52-67	100-114	GRYDILTYGVGLAFDI (SEQ ID NO: 2731)			
044H05	1361	140-248	231-241	1-207	26-35	50-66	99-113	GRYDILTYGVGLAFDI (SEQ ID NO: 2886)			
044H06	1362	141-253	231-241	1-208	26-35	50-66	99-113	GRYDILTYGVGLAFDI (SEQ ID NO: 2886)			



TABLE 1-continued

Clone ID	ssFV SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
103E10	1363	137-248	160-172	188-194	232-237	1-121	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10H	1364	141-253	166-177	193-199	232-242	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2860)
103E10A	1365	147-258	170-183	199-203	238-247	1-131	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2860)
103E10B	1366	141-252	164-176	192-198	231-241	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2860)
103E10C	1367	141-252	164-176	199-199	229-239	1-127	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2860)
103E10D	1368	141-252	164-176	199-199	229-239	1-127	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2860)
103E10E	1369	135-246	158-170	186-192	232-242	1-126	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2860)
103E10F	1370	143-250	164-174	190-196	229-239	1-127	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2860)
103E10G	1371	133-244	156-169	185-191	224-233	1-117	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2860)
103E10H	1372	133-244	156-169	185-191	224-233	1-117	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2860)
103E10I	1373	140-252	163-173	192-198	231-240	1-124	26-34	99-113	EGSSVGAIGALDM (SEQ ID NO: 2852)
103E10J	1374	140-252	163-173	192-198	231-240	1-124	26-34	99-113	EGSSVGAIGALDM (SEQ ID NO: 2852)
103E10K	1375	140-252	163-173	192-198	231-240	1-124	26-34	99-113	EGSSVGAIGALDM (SEQ ID NO: 2852)
103E10L	1376	140-252	163-173	192-198	231-240	1-124	26-34	99-113	EGSSVGAIGALDM (SEQ ID NO: 2852)
103E10M	1377	140-252	163-173	192-198	231-240	1-124	26-34	99-113	EGSSVGAIGALDM (SEQ ID NO: 2852)
103E10N	1378	140-252	163-173	192-198	231-240	1-124	26-34	99-113	EGSSVGAIGALDM (SEQ ID NO: 2852)
103E10O	1379	143-253	165-178	194-200	233-242	1-127	24-33	99-114	ATYDILGYSEGHDI (SEQ ID NO: 2158)
103E10P	1380	143-253	165-178	194-200	233-242	1-127	24-33	99-114	ATYDILGYSEGHDI (SEQ ID NO: 2158)
103E10Q	1381	138-247	159-172	188-194	227-237	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10R	1382	137-247	158-171	188-194	227-237	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10S	1383	141-251	163-176	192-198	231-240	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10T	1384	140-247	161-171	187-193	226-236	1-124	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10U	1385	141-248	164-174	190-196	229-237	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10V	1386	141-248	164-174	190-196	229-237	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10W	1387	141-248	164-174	190-196	229-237	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10X	1388	141-248	164-174	190-196	229-237	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10Y	1389	142-251	163-175	191-197	230-240	1-126	26-35	99-114	ATYDILGYSEGHDI (SEQ ID NO: 2158)
103E10Z	1390	141-251	163-175	192-198	231-240	1-117	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10A	1391	133-240	154-161	180-186	219-229	1-117	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10B	1392	146-256	168-181	197-203	236-245	1-130	26-35	99-112	DAKVPKVALDV (SEQ ID NO: 2823)
103E10C	1393	146-256	168-181	197-203	236-245	1-130	26-35	99-112	DAKVPKVALDV (SEQ ID NO: 2823)
103E10D	1394	145-253	166-176	192-198	231-240	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10E	1395	141-251	163-176	192-198	231-240	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10F	1396	141-251	163-176	192-198	231-240	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10G	1397	141-251	163-176	192-198	231-240	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10H	1398	144-254	166-179	195-201	234-243	1-128	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10I	1399	144-254	166-179	195-201	234-243	1-128	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10J	1400	137-247	158-171	188-194	227-237	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10K	1401	142-252	164-177	189-195	228-237	1-122	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10L	1402	142-252	164-177	189-195	228-237	1-122	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10M	1403	138-248	160-173	189-195	228-237	1-122	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10N	1404	138-248	160-173	189-195	228-237	1-122	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10O	1405	138-248	160-173	189-195	228-237	1-122	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10P	1406	133-244	156-169	185-191	224-233	1-117	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10Q	1407	145-255	167-180	196-202	237-246	1-130	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10R	1408	141-251	163-176	192-198	231-240	1-125	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)
103E10S	1409	146-256	168-181	197-203	236-245	1-130	26-35	99-110	DAKVPKVALDV (SEQ ID NO: 2823)

TABLE 1-continued  
 seqs that immunospecifically bind to B1.6S

Clone ID	seq-F, SEQ ID NO	VL	AA's of VL	AA's of VL CD82	AA's of VH	AA's of VH CD81	AA's of VH CD82	AA's of VH CD83	Sequence (SEQ ID NO)
0064E01	1410	143-250	166-176	192-198	231-239	1-127	26-35	99-116	ETKYSYSSRPVYGMVY (SEQ ID NO: 2756)
0064E02	1411	140-251	162-174	190-196	229-240	1-124	26-35	99-113	RYVYDLTYSRSGP (SEQ ID NO: 2755)
0064E03	1412	144-254	163-175	191-201	234-243	1-128	26-35	99-117	DGVYDLITLVSNGMVDY (SEQ ID NO: 2775)
0064E04	1413	140-250	162-175	191-201	230-239	1-124	26-35	98-113	GERDYDLITLVSNGMVDY (SEQ ID NO: 2948)
0064E05	1414	140-250	162-174	190-196	229-239	1-124	26-35	99-113	ERGYSYSSGSAFV (SEQ ID NO: 2998)
0064E06	1415	145-252	166-176	192-198	231-241	1-126	26-35	99-113	ESGYTSRGRSDYGMVY (SEQ ID NO: 2836)
0064E07	1416	145-252	166-176	192-198	231-241	1-126	26-35	99-113	ESGYTSRGRSDYGMVY (SEQ ID NO: 2900)
0064E08	1417	141-248	163-175	188-194	227-227	1-127	26-35	99-114	DYSHDILITGYSYGMVY (SEQ ID NO: 2795)
0065A12	1418	143-253	165-178	194-200	233-242	1-127	26-35	99-112	QCKNYVSSGYLH (SEQ ID NO: 2916)
0065C04	1419	139-249	161-173	189-195	228-238	1-123	26-35	99-113	QKDYDLITGYSYHFDY (SEQ ID NO: 2908)
0065C09	1420	140-250	162-174	190-196	229-239	1-124	26-35	99-114	ATYDYDLITGYSYHFDY (SEQ ID NO: 2895)
0065C12	1421	140-250	162-174	190-196	229-237	1-123	26-35	99-108	GMGDHYGMVY (SEQ ID NO: 2161)
0065E04	1422	135-247	157-171	188-194	227-236	1-121	26-35	99-110	GMGDHYGMVY (SEQ ID NO: 2161)
0065E04	1423	135-247	157-171	188-194	227-236	1-121	26-35	99-110	GMGDHYGMVY (SEQ ID NO: 2161)
0065G06	1424	135-242	156-166	182-188	221-231	1-119	26-35	99-108	GMGDHYGMVY (SEQ ID NO: 2161)
0065G07	1425	142-249	163-173	189-195	228-238	1-126	26-35	99-115	GMGDHYGMVY (SEQ ID NO: 2161)
0065G08	1426	139-246	160-170	186-192	225-235	1-123	26-35	99-112	SRDILLPHFGMVDY (SEQ ID NO: 2133)
0066A03	1427	144-254	166-179	195-201	234-243	1-128	26-35	99-117	GYFYDYDLITGYNELGAFDI (SEQ ID NO: 2811)
0066A03	1428	144-254	166-179	195-201	234-243	1-128	26-35	99-117	GYFYDYDLITGYNELGAFDI (SEQ ID NO: 2915)
0066A08	1429	137-247	159-171	187-193	226-236	1-121	26-35	99-108	GMGDHYGMVY (SEQ ID NO: 2161)
0066A09	1430	135-245	157-169	185-191	224-234	1-119	26-35	99-108	GMGDHYGMVY (SEQ ID NO: 2161)
0066A10	1431	142-252	164-177	193-199	232-241	1-126	26-35	99-115	DREYDYDLITGYSYGMVY (SEQ ID NO: 2878)
0066A11	1432	143-253	165-178	194-200	233-242	1-127	26-35	99-116	EVRYDYDLITGYSYGMVY (SEQ ID NO: 2778)
0066B01	1433	137-247	159-171	187-193	226-236	1-121	26-35	99-110	AGSSLMYGMVY (SEQ ID NO: 2161)
0066B08	1434	137-247	159-171	187-193	226-236	1-121	26-35	99-110	AGSSLMYGMVY (SEQ ID NO: 2773)
0066B10	1435	142-252	164-177	193-199	232-241	1-126	26-35	99-108	GMGDHYGMVY (SEQ ID NO: 2790)
0066C02	1436	135-245	157-169	185-191	224-234	1-119	26-35	99-108	GMGDHYGMVY (SEQ ID NO: 2153)
0066C11	1437	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDYDLITGYSYHFDY (SEQ ID NO: 2153)
0066C12	1438	135-242	156-166	182-188	221-231	1-119	26-35	99-108	GMGDHYGMVY (SEQ ID NO: 2153)
0066C06	1439	140-250	162-175	191-197	230-239	1-124	26-35	99-113	ENYDYDLITGYSYHFDY (SEQ ID NO: 2772)
0066D01	1440	144-254	166-179	195-201	234-243	1-128	26-35	99-111	ISKEYNNWVADY (SEQ ID NO: 2754)
0066D12	1442	139-249	161-174	190-196	229-238	1-121	26-35	99-112	EGMAYDYDLITGYSYHFDY (SEQ ID NO: 2161)
0066E06	1443	137-247	159-171	187-193	226-236	1-121	26-35	99-110	AGSSLMYGMVY (SEQ ID NO: 2161)
0066E12	1444	135-242	156-166	182-188	221-231	1-119	26-35	99-108	GMGDHYGMVY (SEQ ID NO: 2161)
0066G05	1445	142-249	163-173	189-195	228-238	1-126	26-35	99-115	LYFYDYDLITGYSYHFDY (SEQ ID NO: 2790)
0066G06	1446	144-254	166-179	195-201	234-243	1-128	26-35	99-114	GYFYDYDLITGYSYHFDY (SEQ ID NO: 2791)
0066G12	1447	144-254	166-179	195-201	234-243	1-128	26-35	99-114	GYFYDYDLITGYSYHFDY (SEQ ID NO: 2872)
0066G14	1448	143-254	165-178	194-200	233-243	1-127	26-35	99-116	DRHYDYDLITGYSYHFDY (SEQ ID NO: 2885)
0066H04	1449	143-253	165-178	194-200	233-242	1-127	26-35	99-116	DRHYDYDLITGYSYHFDY (SEQ ID NO: 2885)
0067A07	1450	144-254	166-179	195-201	234-243	1-128	26-35	99-117	VLMGDHYGMVY (SEQ ID NO: 2939)
0067A11	1451	135-245	157-169	186-192	225-234	1-119	26-35	99-108	GMGDHYGMVY (SEQ ID NO: 2161)
0067C05	1452	140-250	162-174	190-196	229-238	1-121	26-35	99-112	EGMAYDYDLITGYSYHFDY (SEQ ID NO: 2161)
0067C08	1453	148-255	171-184	200-206	229-248	1-133	26-35	100-121	ESGYDYDLITGYSYHFDY (SEQ ID NO: 2747)
0067C09	1454	148-255	165-178	194-200	233-242	1-127	26-35	99-110	AGSSLMYGMVY (SEQ ID NO: 2756)
0067D07	1455	137-247	159-171	187-193	226-236	1-121	26-35	99-110	AGSSLMYGMVY (SEQ ID NO: 2773)

TABLE 1-continued  
ssRNA that Immunoprecipitatively Bind to B1a5

Clone ID	ssRNA SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	Sequence (SEQ ID NO)
0607E01	1456	140-248	164-174	190-196	229-238	1-124	26-35	99-113	QDMDILGYGYGMDV (SEQ ID NO: 2921)
0607E06	1457	135-245	157-169	185-191	224-234	1-119	26-35	99-108	GMDHGVGMDV (SEQ ID NO: 2922)
0607E07	1458	150-260	172-184	200-206	239-249	1-134	26-35	100-123	DYTGSEDTLGYGYGMDV (SEQ ID NO: 2926)
0607E08	1459	141-251	163-176	192-198	230-240	1-125	26-35	99-114	ATYDLGYSGDGH (SEQ ID NO: 2155)
0607G03	1460	140-250	162-174	191-197	230-239	1-124	26-35	99-113	ARAVVGLGKNAEL (SEQ ID NO: 2765)
0607G05	1461	140-250	162-174	191-197	230-239	1-124	26-35	99-113	DQHDILGYGYGMDV (SEQ ID NO: 2894)
0607G12	1462	141-251	163-176	192-198	231-241	1-125	26-35	100-119	ATYDLGYSGDGH (SEQ ID NO: 2155)
0607H05	1463	146-256	168-180	196-202	235-245	1-130	26-35	100-119	QDMDILGYGYGMDV (SEQ ID NO: 2926)
0607H06	1464	135-245	157-169	185-191	224-234	1-119	26-35	99-108	GSSONTGYMDV (SEQ ID NO: 2884)
0607H07	1465	137-248	160-172	188-194	227-237	1-121	26-35	99-116	GTGYDLGYGYGSAFDQ (SEQ ID NO: 2800)
0607H08	1466	168-178	186-196	194-200	233-243	1-127	26-35	99-115	GYYVAVGVDGYGYGMDV (SEQ ID NO: 2937)
0608C04	1467	142-254	164-174	190-196	229-240	1-126	26-35	99-113	DIYIMTLAAYYYDS (SEQ ID NO: 2909)
0608C07	1468	140-251	164-174	190-196	229-240	1-126	26-35	99-113	DFYDLGYGMDV (SEQ ID NO: 2846)
0608C08	1469	143-254	166-178	193-199	232-236	1-124	26-35	99-113	DYDLGYGMDV (SEQ ID NO: 2867)
0700F07	1470	140-247	161-171	187-193	226-236	1-124	26-35	99-114	MEYDLGYGYGMDV (SEQ ID NO: 2179)
0700G05	1471	140-250	162-175	191-197	230-239	1-125	26-35	99-114	ATYDLGYSGDGH (SEQ ID NO: 2155)
0700G06	1472	140-250	162-175	191-197	230-239	1-125	26-35	99-116	DMYDLGYTGLAFDM (SEQ ID NO: 2917)
0701A01	1473	141-251	163-176	192-198	231-241	1-126	27-36	99-111	DEGVYGLGYGMDV (SEQ ID NO: 2764)
0701A03	1474	143-250	164-174	190-196	231-241	1-126	27-36	99-111	DEGVYGLGYGMDV (SEQ ID NO: 2771)
0701B08	1475	142-252	164-176	192-198	228-237	1-122	26-35	99-108	SSNPVYGLDV (SEQ ID NO: 2857)
0701E01	1476	138-248	160-173	185-191	224-234	1-119	26-35	99-114	ATYDLGYSGDGH (SEQ ID NO: 2153)
0701F11	1477	135-245	157-169	185-191	223-240	1-125	26-35	99-114	ATYDLGYSGDGH (SEQ ID NO: 2153)
0701F12	1478	141-251	163-176	192-198	231-240	1-125	26-35	99-114	DQMDILGYGYGMDV (SEQ ID NO: 2163)
0701H08	1479	141-251	163-176	192-198	231-240	1-125	26-35	99-114	DRYVYDALGDSYHRAMDV (SEQ ID NO: 2776)
0704A02	1480	147-259	164-174	196-206	237-248	1-131	26-35	99-117	LGKSNILGYTHYGMMDV (SEQ ID NO: 2944)
0704A08	1481	147-259	170-182	194-200	233-244	1-128	26-35	99-117	DOYDLGYSYFDS (SEQ ID NO: 2803)
0704D10	1482	144-253	168-178	194-200	233-244	1-128	26-35	99-116	DOYDLGYGYGSAFDQ (SEQ ID NO: 2800)
0704D01	1483	144-253	168-178	194-200	233-244	1-128	26-35	99-116	DRADILGYGMDV (SEQ ID NO: 2759)
0704E01	1484	140-250	164-174	190-196	229-239	1-124	26-35	99-113	ATYDLGYGMDV (SEQ ID NO: 2755)
0704E08	1485	140-250	164-174	190-196	229-239	1-124	26-35	99-112	ATYDLGYGMDV (SEQ ID NO: 2755)
0704F12	1486	140-250	164-174	190-196	229-239	1-124	26-35	99-115	VSNLDILGYGMDV (SEQ ID NO: 2800)
0704H06	1487	139-251	162-175	191-197	230-240	1-125	26-35	99-115	GTGYDLGYGYGSAFDQ (SEQ ID NO: 2800)
0704H07	1488	143-253	167-177	193-199	232-242	1-127	26-35	99-116	DQRYLDL (SEQ ID NO: 2175)
0704H08	1489	142-254	165-178	194-200	232-242	1-127	26-35	99-106	HLGSLVGGATGALDM (SEQ ID NO: 2174)
0705A07	1490	143-253	167-177	193-199	232-242	1-127	26-35	99-113	HLGSLVGGATGALDM (SEQ ID NO: 2800)
0705A08	1491	143-253	167-177	193-199	232-242	1-127	26-35	99-113	ATYDLGYGMDV (SEQ ID NO: 2800)
0705B04	1492	133-247	156-168	184-190	223-233	1-117	26-35	99-114	ATYDLGYGMDV (SEQ ID NO: 2800)
0705B06	1493	140-252	163-175	191-197	231-241	1-127	26-35	99-113	SOYDLGYGMDV (SEQ ID NO: 2812)
0705B08	1494	143-257	166-179	194-201	234-246	1-131	26-35	99-113	GREDTGVKVPWRTHYHYGMDV (SEQ ID NO: 2835)
0705B09	1495	141-252	164-176	192-198	231-240	1-124	26-35	99-113	DQRYLDL (SEQ ID NO: 2175)
0705B12	1496	140-251	163-176	192-198	231-240	1-124	26-35	99-106	GTGYDLGYGYGMDV (SEQ ID NO: 2800)
0705B17	1497	147-259	170-183	195-205	238-248	1-131	26-35	99-116	STYDLGYGMDV (SEQ ID NO: 2883)
0705C05	1498	143-253	168-178	193-199	232-233	1-117	26-35	99-116	GTGYDLGYGYGMDV (SEQ ID NO: 2800)
0705C06	1499	143-253	168-178	193-199	232-233	1-117	26-35	99-116	GTGYDLGYGYGMDV (SEQ ID NO: 2800)
0705D05	1500	141-252	164-176	192-198	231-241	1-125	26-35	99-113	HLGSLVGGATGALDM (SEQ ID NO: 2174)
0705D08	1501	140-251	163-175	191-197	230-240	1-124	26-34	99-113	HLGSLVGGATGALDM (SEQ ID NO: 2174)

TABLE 1—continued

seqId that Immunogenically Bind to B1as									
Close ID	seqId NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	Sequence (SEQ ID NO)	
075F5001	1502	143-253	167-177	191-199	232-242	1-127	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2800)	
075F5001	1503	148-261	172-184	200-206	239-250	1-127	28-37	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2801)	
075F5004	1504	143-253	166-179	195-201	231-244	1-127	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2802)	
075F5004	1505	140-252	163-176	192-201	234-244	1-127	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2803)	
075F5010	1506	140-252	163-176	192-201	234-244	1-127	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2804)	
075F5011	1507	133-244	156-168	194-200	233-241	1-124	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2805)	
075F5012	1508	142-254	165-178	194-200	233-241	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2806)	
075F502	1509	144-251	168-176	194-200	233-242	1-128	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2807)	
075F504	1510	141-253	164-175	192-198	231-240	1-128	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2808)	
075F506	1511	144-254	168-178	194-200	233-240	1-124	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2809)	
075F508	1512	133-244	163-175	191-197	232-233	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2810)	
075F508	1513	133-244	163-175	191-197	232-233	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2811)	
075F509	1514	145-257	168-181	197-203	232-232	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2812)	
075F510	1515	133-243	157-167	183-189	222-232	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2813)	
075F511	1516	133-245	156-169	185-191	224-234	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2814)	
075F505	1517	140-252	163-175	191-197	230-241	1-124	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2815)	
075F508	1518	140-252	163-175	191-197	230-241	1-124	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2816)	
075F508	1519	140-252	163-175	192-198	231-241	1-124	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2817)	
075G211	1520	141-253	164-177	195-201	234-243	1-127	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2818)	
075G12	1521	133-245	156-169	185-191	224-232	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2819)	
075H02	1522	143-254	166-178	194-200	233-243	1-127	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2820)	
075H03	1523	133-245	156-169	185-191	224-234	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2821)	
075H06	1524	133-244	156-168	184-190	223-233	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2822)	
075H06	1525	133-244	156-168	184-190	223-233	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2823)	
076A01	1526	142-253	166-179	195-201	234-243	1-127	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2824)	
076A03	1527	133-247	159-171	187-193	226-234	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2825)	
076A06	1528	133-245	156-168	184-190	229-239	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2826)	
076A07	1529	139-250	162-174	190-196	229-239	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2827)	
076A08	1530	142-253	166-176	192-198	231-242	1-126	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2828)	
076B01	1531	141-252	165-177	195-201	236-246	1-127	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2829)	
076B03	1532	133-247	157-169	183-189	222-231	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2830)	
076B07	1533	133-243	157-167	183-189	222-231	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2831)	
076B08	1534	141-252	166-177	193-199	232-241	1-125	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2832)	
076C04	1535	140-250	164-174	190-196	229-239	1-124	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2833)	
076C10	1536	140-251	163-175	191-197	230-240	1-124	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2834)	
076C10	1537	141-252	164-176	192-198	231-241	1-125	26-37	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2835)	
076C08	1538	141-252	164-176	192-198	231-241	1-125	26-37	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2836)	
076D01	1539	143-253	166-179	194-201	232-240	1-124	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2837)	
076D11	1540	143-252	167-177	193-199	232-241	1-127	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2838)	
076D04	1541	143-252	167-177	193-199	232-240	1-124	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2839)	
076D07	1542	140-251	163-175	191-197	232-241	1-125	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2840)	
076D09	1543	141-253	164-177	193-199	232-243	1-127	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2841)	
076D11	1544	140-251	163-175	191-197	234-243	1-127	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2842)	
076D01	1545	143-253	166-179	194-201	232-240	1-124	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2843)	
076D03	1546	140-251	163-175	191-197	234-243	1-127	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2844)	
076D04	1547	133-245	157-169	185-191	224-234	1-117	26-35	GVYDILVYVYMGSAFDQ (SEQ ID NO: 2845)	

TABLE 1-continued

ssFw that Immunogenically Bind to BLyS									
Clone ID	ssFw SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)	AAs of VH CDR3
1076F08	1548	140-250	164-174	190-196	239-239	1-124	26-36	VFPTLPGYHMAETI (SEQ ID NO: 2730)	98-113
1076F10	1549	140-252	163-175	191-197	230-241	1-124	26-34	ELGSLVGGTGLDM (SEQ ID NO: 2174)	98-113
1076G09	1550	133-245	156-168	184-190	232-234	1-117	26-35	DOGRYLDL (SEQ ID NO: 2175)	99-106
1076G10	1551	140-251	163-175	191-197	230-240	1-124	26-35	GRVYDMLTGGGVDF (SEQ ID NO: 2858)	99-113
1076G11	1552	140-251	163-175	192-198	230-240	1-124	26-35	GTVDILTYGWSAKAFQ (SEQ ID NO: 2800)	99-116
1076G12	1553	146-257	168-181	195-205	240-248	1-127	26-35	NGYYDILTYGWSYGGMDV (SEQ ID NO: 2769)	99-116
1076H02	1554	140-251	163-175	191-197	230-240	1-124	26-35	INVDILTYGWSYGGMDV (SEQ ID NO: 2871)	99-113
1076H04	1555	141-251	163-175	191-197	230-240	1-125	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2865)	99-113
1076H05	1556	140-251	163-175	191-197	230-240	1-124	26-35	VPYDILTYGWSYGGMDV (SEQ ID NO: 2871)	99-113
1076H06	1557	140-252	163-176	192-198	231-241	1-124	26-35	GSQYDILTYGWSYGGMDV (SEQ ID NO: 2766)	99-116
1076H07	1558	140-252	163-176	192-198	231-241	1-127	26-35	GSQYDILTYGWSYGGMDV (SEQ ID NO: 2766)	99-116
1076H08	1559	143-256	166-179	195-201	234-245	1-127	26-35	YYDILTYGWSYGGMDV (SEQ ID NO: 2177)	99-113
1076H10	1560	140-250	162-175	191-197	230-239	1-124	26-35	MFYDILTYGWSYGGMDV (SEQ ID NO: 2871)	99-114
1076H04	1561	140-250	162-175	191-197	230-239	1-125	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-114
1076H01	1562	141-251	164-174	192-198	231-240	1-125	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-114
1076H01-K	1563	141-250	164-174	190-196	229-239	1-125	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-114
1076H01-L	1564	141-250	164-174	192-198	231-239	1-125	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-114
1076H01-R	1565	141-250	164-176	192-198	231-239	1-125	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-114
1076H04-R	1566	141-250	164-176	192-198	231-239	1-133	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-114
1076H10	1567	149-259	171-183	199-205	238-248	1-133	26-35	DOGRYLDL (SEQ ID NO: 2175)	99-106
1068C06	1568	133-244	156-169	185-191	224-233	1-117	26-35	DOGRYLDL (SEQ ID NO: 2175)	99-106
1073E12	1569	133-244	156-168	184-190	223-233	1-117	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1073E12	1570	140-249	163-173	189-195	228-238	1-124	26-34	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1075H06	1571	140-249	163-173	191-197	230-238	1-124	26-34	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1075H09	1572	140-249	163-175	191-197	230-238	1-124	26-34	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1026C04	1573	140-249	163-175	191-197	230-238	1-124	26-34	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1072B12	1574	141-250	164-174	190-196	229-239	1-125	26-34	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1030A10	1575	140-252	163-176	192-198	231-241	1-124	26-34	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1030A10	1576	147-257	169-182	196-204	237-246	1-131	26-35	DOGRYLDL (SEQ ID NO: 2175)	99-113
1064C07	1577	147-257	169-182	196-204	237-246	1-131	26-35	DOGRYLDL (SEQ ID NO: 2175)	99-113
1064C07	1578	144-254	157-167	181-189	222-230	1-128	26-36	DOGRYLDL (SEQ ID NO: 2175)	99-113
1065D04	1579	147-257	169-182	196-204	237-246	1-131	26-35	DOGRYLDL (SEQ ID NO: 2175)	99-113
1065D08	1580	135-242	158-168	184-190	223-231	1-119	26-35	DOGRYLDL (SEQ ID NO: 2175)	99-113
1067F05	1581	140-250	156-168	184-190	230-239	1-124	26-35	DOGRYLDL (SEQ ID NO: 2175)	99-113
1068D04	1582	133-244	156-168	184-190	223-233	1-117	26-35	DOGRYLDL (SEQ ID NO: 2175)	99-113
1068D04	1583	133-244	156-168	184-190	223-233	1-117	26-35	DOGRYLDL (SEQ ID NO: 2175)	99-113
1068C08	1584	140-252	163-175	191-197	231-241	1-124	26-34	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1068C08	1585	139-251	162-175	191-197	231-241	1-126	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1068F03	1586	141-251	163-176	192-198	231-240	1-125	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1069H07	1587	141-251	163-176	192-198	231-240	1-125	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1071B03	1588	141-248	162-172	188-194	227-237	1-125	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1073B09	1589	136-246	158-171	187-193	226-235	1-120	26-34	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1074B12	1590	140-251	163-176	192-198	231-241	1-124	26-34	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1075G01	1591	140-251	163-174	190-196	229-240	1-124	26-34	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1075G01	1592	140-251	163-174	190-196	229-240	1-124	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113
1078D02	1593	140-250	162-175	191-197	230-239	1-124	26-35	ELGSLVGGTGLDM (SEQ ID NO: 2174)	99-113

TABLE 1-continued

Clone ID	sFv SEQ ID NO	sFv that Immunogenetically Bind to B1a5									
		AA# of VL	AA# of VL CDR1	AA# of VL CDR2	AA# of VH	AA# of VH CDR1	AA# of VH CDR2	AA# of VH CDR3	AA# of VH CDR3	VH CDR3 Sequence (SEQ ID NO)	
1078D08	1594	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	DAQSYDILGYSVAFDI (SEQ ID NO: 2183)	
1078D08	1595	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	VYDYLGNLFSDY (SEQ ID NO: 2177)	
1064A01	1596	150-257	171-181	197-203	236-246	1-134	26-35	50-66	99-123	GPSTIYDILGITYPTYYTYADY (SEQ ID NO: 3014)	
1064A03	1597	145-255	167-179	195-201	234-244	1-129	26-35	52-67	100-118	HVYDYLIGYVGRHYDY (SEQ ID NO: 2167)	
1064B05	1598	140-250	160-174	190-196	229-239	1-124	26-35	50-66	99-113	BRGVYVAGSFDL (SEQ ID NO: 2885)	
1064B11	1599	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-113	DRGVLLSSFFS (SEQ ID NO: 3033)	
1064C02	1600	146-256	168-180	196-202	235-245	1-130	26-35	50-66	99-119	BEYDYLIGYVGRHYDY (SEQ ID NO: 3068)	
1064C03	1601	146-256	168-180	196-202	235-245	1-130	26-35	50-66	99-113	BEYDYLIGYVGRHYDY (SEQ ID NO: 2985)	
1064C11	1602	143-253	166-178	194-200	233-242	1-127	26-35	50-65	98-116	DYVYDHLIGVAGHADI (SEQ ID NO: 3055)	
1064C12	1603	148-255	171-181	197-203	236-244	1-132	26-37	52-69	102-112	ESGRVYDILGYSGGGMDV (SEQ ID NO: 3052)	
1064D04	1604	146-256	168-181	197-203	236-245	1-132	26-35	50-66	99-119	DGANNYDILGITYTYVGMV (SEQ ID NO: 3072)	
1064D04	1605	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-107	RSYDILGITYTYGMV (SEQ ID NO: 3090)	
1064D06	1606	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-104	EGSGYVAVG (SEQ ID NO: 2981)	
1064D06	1607	146-256	168-180	196-202	235-244	1-130	26-37	52-67	100-119	KRGQYDILGITYVGRHYDY (SEQ ID NO: 3088)	
1064E07	1608	145-255	167-180	196-202	235-245	1-129	26-35	50-66	99-118	BRGVYDILGITYVGRHYDY (SEQ ID NO: 3053)	
1064F09	1609	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLGYSFGEDI (SEQ ID NO: 2153)	
1064F09	1610	147-253	169-181	197-203	236-246	1-131	26-35	50-66	99-120	ATYDPLGYSFGEDI (SEQ ID NO: 2988)	
1064F10	1611	143-253	165-177	193-199	232-242	1-127	26-35	50-66	98-116	DTLGYDILGYPYTYTYMDV (SEQ ID NO: 2988)	
1064F11	1612	142-252	164-177	193-199	232-241	1-126	26-35	50-65	98-115	GRHYDILGITYNEADI (SEQ ID NO: 3031)	
1064G01	1613	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	NYDYLIGYTYGMV (SEQ ID NO: 3077)	
1064G01	1614	133-243	155-167	183-189	222-232	1-117	26-35	50-66	99-106	DSNGSYTY (SEQ ID NO: 3044)	
1064G08	1615	138-245	159-169	185-191	234-241	1-122	26-35	50-66	99-111	GGVTAGRSYVTER (SEQ ID NO: 2990)	
1064G10	1616	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	SPNGSYGVAVGLE (SEQ ID NO: 3085)	
1064G11	1617	138-248	160-173	189-195	228-237	1-122	26-35	50-65	98-111	YFDGSGYVPSY (SEQ ID NO: 3064)	
1064G12	1618	138-249	160-173	189-195	228-238	1-123	26-35	50-65	98-112	VNYDILGITYTYDY (SEQ ID NO: 3049)	
1064H03	1619	142-253	168-178	194-200	233-242	1-127	26-37	52-67	100-116	VALLGRYDILGITYTYDY (SEQ ID NO: 2989)	
1064H03	1620	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	PLGTVAKASVAFDI (SEQ ID NO: 2929)	
1064H06	1621	149-256	170-180	196-202	235-245	1-133	26-35	50-66	99-122	DRGANNYDILGYPYTYTYMDV (SEQ ID NO: 2969)	
1065A02	1622	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLGYSFGEDI (SEQ ID NO: 2153)	
1065A04	1623	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLGYSFGEDI (SEQ ID NO: 2153)	
1065A06	1624	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLGYSFGEDI (SEQ ID NO: 2153)	
1065A07	1625	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DGAGYDILGITYTYGMV (SEQ ID NO: 3087)	
1065B04	1626	145-255	167-180	196-202	235-244	1-129	26-35	50-65	98-118	WATYDILGITYVGRHYADI (SEQ ID NO: 3073)	
1065B09	1627	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	SPDILGITYTYTYDY (SEQ ID NO: 3032)	
1065B12	1628	146-253	167-177	193-199	232-242	1-130	26-35	50-66	99-119	DAGHSYDILGITYTYGMV (SEQ ID NO: 2966)	
1065C02	1629	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-112	EGGAYLVNGYVQR (SEQ ID NO: 2815)	
1065C06	1630	136-246	158-170	186-192	225-235	1-120	26-35	50-66	99-109	EGGSWLDLY (SEQ ID NO: 3007)	
1065C06	1631	141-253	163-175	191-197	230-242	1-125	26-35	50-66	99-114	ATYDPLGYSFGEDI (SEQ ID NO: 2153)	
1065C08	1632	141-250	163-176	192-198	231-239	1-125	26-35	50-66	99-114	VGVNSYHESYEDMDV (SEQ ID NO: 3153)	
1065C10	1633	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	CGAGCTSPRLDY (SEQ ID NO: 3002)	
1065D01	1634	142-252	164-177	193-199	233-241	1-126	26-35	50-66	99-115	DRYDILGITYTYGMV (SEQ ID NO: 3074)	
1065D03	1635	142-249	165-175	191-197	230-238	1-126	26-35	50-66	99-115	AFYDILGITYTYGMV (SEQ ID NO: 3028)	
1065D05	1636	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	KRDYDILGITYTYGMV (SEQ ID NO: 3040)	
1065D06	1637	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	DPNYDILGITYTYGMV (SEQ ID NO: 3062)	
1065D07	1638	139-246	160-173	186-192	222-233	1-123	26-35	50-66	99-112	EPQQLARGHMDV (SEQ ID NO: 3027)	
1065D05	1639	137-244	158-168	184-190	222-233	1-121	26-35	50-66	99-110	AGSLATGVTDV (SEQ ID NO: 2773)	

### Effect of Fcγ that Immunospecifically Bind to BLYS

[illegible]

TABLE 1-continued  
seqs that Immunoreactively Bind to BLyS

TABLE 1-continued									
Clone ID	seqV SEQ ID NO	seqV that Immunoprecipitates Bind to B125							
		AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3
1686	133-244	156-169	185-191	224-233	1-117	26-35	50-66	99-106	DWGHWFDP (SEQ ID NO: 2982)
1687	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	SGSLMTYGVSTYV (SEQ ID NO: 3015)
1688	141-251	163-176	192-198	230-240	1-125	26-35	50-66	99-114	EPYDITGVGVSTYV (SEQ ID NO: 3041)
1689	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSLMTYGVSTYV (SEQ ID NO: 2773)
1690	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-109	TSRVRGVTDL (SEQ ID NO: 3020)
1691	136-246	158-171	187-193	226-235	1-121	26-35	50-66	99-110	AGSLMTYGVTDL (SEQ ID NO: 2773)
1692	137-244	158-168	184-190	235-245	1-130	26-35	50-66	99-119	EGSSGSRGSRQKPPV (SEQ ID NO: 2993)
1693	146-256	168-180	184-190	233-243	1-121	26-35	50-66	99-110	AGSLMTYGVSTYV (SEQ ID NO: 2773)
1694	137-247	156-171	184-190	232-241	1-126	26-35	50-66	99-110	QGGSYDSPLDV (SEQ ID NO: 2860)
1695	137-247	156-171	184-190	232-241	1-126	26-35	50-66	99-110	QGGSYDSPLDV (SEQ ID NO: 3002)
1696	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSLMTYGVSTYV (SEQ ID NO: 2773)
1697	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-111	DYRVDITGVGVSTYV (SEQ ID NO: 2996)
1698	144-252	164-176	192-198	231-241	1-128	26-35	50-66	99-117	QHYDITGVGVSTYV (SEQ ID NO: 3007)
1699	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DYRVDITGVGVSTYV (SEQ ID NO: 3007)
1700	141-248	164-174	192-198	231-241	1-126	26-35	50-66	99-114	QHYDITGVGVSTYV (SEQ ID NO: 3015)
1701	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DYRVDITGVGVSTYV (SEQ ID NO: 3015)
1702	140-248	160-170	186-192	225-235	1-123	26-35	50-66	99-113	AGSLMTYGVSTYV (SEQ ID NO: 3039)
1703	140-247	160-171	187-193	226-236	1-124	26-35	50-66	99-110	AGSLMTYGVSTYV (SEQ ID NO: 3016)
1704	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-113	ENYDITGVGVSTYV (SEQ ID NO: 2773)
1705	140-248	161-171	187-193	228-236	1-124	26-35	50-66	99-110	AGSLMTYGVSTYV (SEQ ID NO: 3015)
1706	141-251	163-176	192-198	230-240	1-125	26-35	50-66	99-110	AGSLMTYGVSTYV (SEQ ID NO: 3015)
1707	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSLMTYGVSTYV (SEQ ID NO: 2979)
1708	142-254	165-178	193-199	236-246	1-128	26-35	50-66	99-120	TRGKAGQTRARWGDV (SEQ ID NO: 2869)
1709	141-251	163-176	192-198	230-240	1-125	26-35	50-66	99-110	AGSLMTYGVSTYV (SEQ ID NO: 2869)
1710	147-257	170-183	199-205	238-246	1-131	26-35	50-66	99-106	GRDGTGKVPKQVHYHYVMDV (SEQ ID NO: 2869)
1711	133-247	157-169	185-191	223-232	1-119	26-35	49-65	99-113	DQKDYDL (SEQ ID NO: 2175)
1712	140-251	163-176	192-198	230-240	1-125	26-35	50-66	99-114	ELGSLVGVSTYV (SEQ ID NO: 2174)
1713	141-252	164-176	192-198	230-240	1-125	26-35	50-66	99-108	ELGRLGEGVYVSTYV (SEQ ID NO: 2838)
1714	135-245	157-169	185-191	223-232	1-119	26-35	50-66	99-110	KNRQVGVSTYV (SEQ ID NO: 2843)
1715	140-251	163-176	192-198	230-240	1-125	26-35	50-66	99-114	ESGSLVGVSTYV (SEQ ID NO: 3044)
1716	140-251	163-176	192-198	230-240	1-125	26-35	50-66	99-114	ESGSLVGVSTYV (SEQ ID NO: 3044)
1717	141-248	162-171	188-194	228-236	1-124	26-35	50-66	99-114	MEYDITGVGVSTYV (SEQ ID NO: 2179)
1718	141-248	162-171	188-194	228-236	1-124	26-35	50-66	99-114	MEYDITGVGVSTYV (SEQ ID NO: 2179)
1719	141-248	162-171	188-194	228-236	1-124	26-35	50-66	99-112	PYDITGVGVSTYV (SEQ ID NO: 2179)
1720	139-249	161-171	187-193	227-235	1-123	26-35	50-66	99-112	PYDITGVGVSTYV (SEQ ID NO: 2179)
1721	141-248	162-171	188-194	228-236	1-124	26-35	50-66	99-116	VLPYDITGVGVSTYV (SEQ ID NO: 3000)
1722	141-248	162-171	188-194	228-236	1-124	26-35	50-66	99-115	DQYDITGVGVSTYV (SEQ ID NO: 2115)
1723	142-250	163-173	189-195	229-239	1-127	26-35	50-66	99-115	DQYDITGVGVSTYV (SEQ ID NO: 2115)
1724	142-249	163-173	189-195	229-239	1-127	26-35	50-66	99-113	YVYDITGVGVSTYV (SEQ ID NO: 2179)
1725	142-249	163-173	189-195	229-239	1-127	26-35	50-66	99-113	YVYDITGVGVSTYV (SEQ ID NO: 2179)
1726	140-247	161-171	187-193	227-235	1-123	26-35	50-66	99-114	MEYDITGVGVSTYV (SEQ ID NO: 3051)
1727	141-248	161-171	187-193	227-235	1-123	26-35	50-66	99-114	MEYDITGVGVSTYV (SEQ ID NO: 3051)
1728	140-247	161-171	187-193	227-235	1-123	26-35	50-66	99-115	DQYDITGVGVSTYV (SEQ ID NO: 3059)
1729	140-247	161-171	187-193	227-235	1-123	26-35	50-66	99-118	DRLEYDITGVGVSTYV (SEQ ID NO: 3039)
1730	142-249	163-173	189-195	229-239	1-127	26-35	50-66	99-118	DRLEYDITGVGVSTYV (SEQ ID NO: 3039)
1731	145-252	166-176	192-198	231-241	1-126	26-35	50-66	99-118	DRLEYDITGVGVSTYV (SEQ ID NO: 3039)



TABLE 1-continued

Clone ID	gsFv SEQ ID NO	seqs that immunospecifically bind to BLyS									
		AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)	
060G11	1732	141-248	162-172	186-194	227-237	1-125	26-35	50-66	99-114	MEYDLTYGGGVYD (SEQ ID NO: 2179)	
070A009	1733	141-248	162-172	190-196	229-237	1-125	26-35	50-66	99-114	MEYDLTYGGGVYD (SEQ ID NO: 2179)	
070B001	1734	141-248	162-172	186-194	227-237	1-125	26-35	50-66	99-114	MEYDLTYGGGVYD (SEQ ID NO: 2179)	
070B005	1735	144-254	166-179	192-201	234-243	1-128	26-35	50-66	99-114	SQSYDLITGGGVYGMV (SEQ ID NO: 3038)	
070B005	1736	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDLTYGGGVYD (SEQ ID NO: 2179)	
070B005	1737	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDLTYGGGVYD (SEQ ID NO: 2179)	
070B005	1738	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	SQSYDLITGGGVYGMV (SEQ ID NO: 3034)	
070B001	1739	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	SQSYDLITGGGVYGMV (SEQ ID NO: 3038)	
070B001	1740	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	SQSYDLITGGGVYGMV (SEQ ID NO: 3067)	
070G101	1741	141-248	162-172	186-194	229-237	1-125	26-35	50-66	99-114	MEYDLTYGGGVYD (SEQ ID NO: 2179)	
070G106	1742	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108	GMEDHYGMV (SEQ ID NO: 2161)	
070B002	1743	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108	GMEDHYGMV (SEQ ID NO: 2161)	
070B002	1744	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGTSLMNYGTDV (SEQ ID NO: 3048)	
070B002	1745	146-256	168-181	197-205	236-245	1-130	26-37	52-66	99-119	VPYVYDSGGVGLYGVYGMV (SEQ ID NO: 3030)	
070B002	1746	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGTSLMNYGTDV (SEQ ID NO: 3048)	
070B002	1747	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070A001	1748	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-112	SRDLLLPHFYGMV (SEQ ID NO: 2133)	
070A009	1749	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070B002	1750	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108	GMEDHYGMV (SEQ ID NO: 2161)	
070B002	1751	137-247	159-172	186-194	227-236	1-121	26-35	50-66	99-110	AGTSLMNYGTDV (SEQ ID NO: 3031)	
070B011	1752	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070B012	1753	140-249	162-173	189-195	228-238	1-124	26-35	50-66	99-113	ENYDITLYTGAFDI (SEQ ID NO: 2995)	
070C005	1754	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108	GMEDHYGMV (SEQ ID NO: 2161)	
070C010	1755	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070D001	1756	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070D001	1757	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108	GMEDHYGMV (SEQ ID NO: 2161)	
070E001	1758	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070E004	1759	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EGSYDLITGGGVYGMV (SEQ ID NO: 2171)	
070E005	1760	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070E006	1761	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108	GMEDHYGMV (SEQ ID NO: 2161)	
070F003	1762	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108	GMEDHYGMV (SEQ ID NO: 2161)	
070F003	1763	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070F011	1764	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	EDYDITLLTCAQMV (SEQ ID NO: 2983)	
070F011	1765	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070G004	1766	137-247	159-171	187-193	226-236	1-121	26-35	50-68	101-110	RDITLTYDS (SEQ ID NO: 2933)	
070G005	1767	137-247	159-171	187-193	226-236	1-121	26-35	50-68	99-110	GYRNDWYGAFDI (SEQ ID NO: 3079)	
070G009	1768	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070H001	1769	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070H001	1770	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGTSLMNYGTDV (SEQ ID NO: 3070)	
070A002	1771	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	GYDITLYTGAFDI (SEQ ID NO: 2988)	
070A003	1772	142-252	164-177	193-199	233-241	1-126	26-35	50-66	99-121	TVQMDSEYTLTGNGVYD (SEQ ID NO: 3019)	
070A004	1773	148-258	170-183	199-205	238-247	1-132	26-35	50-66	99-121	YQMDSEYTLTGNGVYD (SEQ ID NO: 2132)	
070A005	1774	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070A006	1775	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070A006	1776	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTYSSEKGF (SEQ ID NO: 2153)	
070A010	1777	146-253	167-177	193-199	232-242	1-130	26-35	50-66	99-119	GMEDHYGMV (SEQ ID NO: 3082)	

TABLE 1-continued

sequence that immunospecifically bind to BLIS									
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
073A11	1778	141-248	164-174	190-196	229-237	1-125	26-35	99-114	SYVDILTYGYPGMDV (SEQ ID NO: 3004)
073B05	1779	144-254	166-176	195-201	234-241	1-128	26-35	99-114	DLWYYDILTYGLDADF (SEQ ID NO: 2999)
073B06	1780	144-254	166-176	195-201	234-241	1-128	26-35	99-114	DLWYYDILTYGLDADF (SEQ ID NO: 2999)
073B06	1781	139-246	160-170	186-192	225-235	1-123	26-35	99-111	SRDLLLPHYGMDV (SEQ ID NO: 2999)
073B07	1782	138-248	160-173	189-195	228-237	1-122	26-35	99-111	TRADVILTRYSDP (SEQ ID NO: 2750)
073B08	1783	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073B09	1784	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073C01	1785	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073C02	1786	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073C03	1787	148-255	169-179	188-194	224-244	1-132	26-35	99-121	QAMDSYVLLITGNGVYFDY (SEQ ID NO: 3076)
073C04	1788	141-252	164-177	193-199	232-241	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073C07	1789	141-252	164-177	193-199	232-241	1-125	26-35	99-114	GMEDHYGMDV (SEQ ID NO: 3008)
073C08	1790	142-252	164-177	193-199	232-241	1-126	26-35	99-114	EMGYDILTYGLTYMDV (SEQ ID NO: 2862)
073C09	1791	141-252	163-176	192-198	231-240	1-125	26-35	99-114	QHYDILTYGSPDFDI (SEQ ID NO: 3022)
073C10	1792	141-251	163-176	192-198	231-240	1-125	26-35	99-114	QHYDILTYGSPDFDI (SEQ ID NO: 3022)
073C12	1793	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073D01	1794	135-245	157-169	185-191	224-234	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073D03	1795	141-251	163-176	192-198	231-240	1-125	26-35	99-114	GMEDHYGMDV (SEQ ID NO: 2161)
073D06	1796	144-254	166-179	195-201	234-243	1-128	26-35	99-117	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073D08	1797	144-254	166-179	195-201	234-243	1-128	26-35	99-117	EVRYDILTYSLAGLDN (SEQ ID NO: 2751)
073D09	1798	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073D11	1799	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073E01	1800	148-258	170-183	199-205	238-247	1-132	26-37	102-121	EGAHYDILGHVYTHYGMVDV (SEQ ID NO: 2747)
073E02	1801	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073E03	1802	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 3003)
073E04	1803	141-251	163-176	192-198	231-240	1-125	26-35	99-114	QHYDILTYGSPDFDI (SEQ ID NO: 3022)
073E06	1804	140-250	162-175	191-197	230-239	1-124	26-35	99-113	EVRYDILTYSLAGLDN (SEQ ID NO: 2751)
073F01	1805	141-251	163-175	191-197	230-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073F02	1806	141-251	163-175	191-197	230-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073F03	1807	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073F05	1808	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073F06	1809	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073F09	1810	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073F11	1811	141-251	163-175	191-197	230-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073F12	1812	141-251	163-176	192-198	231-240	1-125	26-35	99-114	DGSDYDILTYGTYMDV (SEQ ID NO: 2154)
073G03	1813	143-253	165-178	194-200	233-242	1-127	26-35	99-116	GEGYDILTYGLTYGMVDV (SEQ ID NO: 3037)
073G04	1814	143-253	165-178	194-200	233-242	1-127	26-35	99-116	GEGYDILTYGLTYGMVDV (SEQ ID NO: 3037)
073G05	1815	135-248	157-169	188-191	224-234	1-119	26-35	99-108	GMEDHYGMDV (SEQ ID NO: 2160)
073G06	1816	135-248	157-169	188-191	224-234	1-119	26-35	99-108	GMEDHYGMDV (SEQ ID NO: 2160)
073G07	1817	142-249	163-172	188-195	228-238	1-126	26-35	99-115	GSYDILTYGSSIGMDV (SEQ ID NO: 3063)
073G08	1818	139-246	160-170	186-192	225-235	1-123	26-35	99-112	SRDLLLPHYGMDV (SEQ ID NO: 2153)
073G09	1819	145-255	167-180	196-202	235-244	1-129	26-35	99-118	DRGHVYDILTYGTYBSCDY (SEQ ID NO: 3061)
073G10	1820	135-245	157-170	186-192	225-234	1-121	26-35	99-108	GMEDHYGMDV (SEQ ID NO: 2749)
073G12	1821	142-252	164-177	193-199	232-241	1-126	26-35	101-115	GMEDHYGMDV (SEQ ID NO: 3083)
073G13	1822	141-251	163-176	192-198	231-240	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)
073H03	1823	141-248	162-172	188-194	227-237	1-125	26-35	99-114	ATYDPLTYSDEGDI (SEQ ID NO: 2153)

TABLE 1-continued  
 scFvs that Immunospecifically Bind to B125

Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
073H05	1824	141-251	163-176	192-198	231-240	35-35	98-114	ATPTPTGTSPTGPT (SEQ ID NO: 2153)
073H06	1825	141-251	163-176	192-198	231-240	35-35	98-114	ATPTPTGTSPTGPT (SEQ ID NO: 2153)
073H07	1826	138-245	159-169	185-191	224-234	1-125	99-111	TYDILITGYTDFY (SEQ ID NO: 3056)
073H08	1827	141-251	163-176	192-198	231-240	1-125	99-114	ATYDILITGYTDFY (SEQ ID NO: 2153)
074A05	1828	143-253	167-179	195-201	234-244	1-127	99-116	LPPTDLSRGSADAFY (SEQ ID NO: 3060)
074A06	1829	143-253	167-179	195-201	234-244	1-127	99-116	LPPTDLSRGSADAFY (SEQ ID NO: 3065)
074B01	1830	138-245	159-169	185-191	224-234	1-117	99-106	DQGRYLDL (SEQ ID NO: 2175)
074B02	1831	138-245	159-169	185-191	224-234	1-117	99-106	DQGRYLDL (SEQ ID NO: 2175)
074B03	1832	140-251	163-175	191-197	230-240	1-124	98-113	EGSLTSGATGALDM (SEQ ID NO: 2174)
074B04	1833	141-251	165-175	191-197	230-240	1-125	99-114	GGYDILITGYTDFY (SEQ ID NO: 2175)
074B05	1834	133-246	156-169	185-191	224-235	1-117	99-106	DQGRYLDL (SEQ ID NO: 2175)
074B06	1835	143-253	167-177	195-199	232-242	1-127	99-116	DRYDILITGDTYGGYGMV (SEQ ID NO: 3060)
074B07	1836	150-262	173-186	202-208	241-251	1-134	99-123	VQGGTYDILITGYTGGPKDILYGMV (SEQ ID NO: 3061)
074B08	1837	140-251	163-175	191-197	230-240	1-124	98-113	ELGSLTSGATGALDM (SEQ ID NO: 2175)
074B09	1838	138-249	161-174	190-196	229-238	1-122	99-111	ESGGYTNFQY (SEQ ID NO: 2991)
074B10	1839	133-245	156-169	185-191	224-234	1-117	99-106	DQGRYLDL (SEQ ID NO: 2175)
074B11	1840	140-251	163-175	191-197	230-240	1-124	98-113	ELGSLTSGATGALDM (SEQ ID NO: 2174)
074B12	1841	146-258	169-182	198-204	237-247	1-130	101-119	DPGNIDILITGYTGGYGMV (SEQ ID NO: 2935)
074B13	1842	140-251	163-175	191-197	230-240	1-124	98-113	ELGSLTSGATGALDM (SEQ ID NO: 2174)
074B14	1843	143-254	166-178	194-200	233-243	1-121	99-110	ESSTLTPYTYGGYGMV (SEQ ID NO: 3035)
074B15	1844	133-242	158-168	184-190	224-231	1-117	99-106	DQGRYLDL (SEQ ID NO: 2175)
074A10	1845	133-244	157-169	185-191	224-233	1-117	99-106	DQGRYLDL (SEQ ID NO: 2175)
074A11	1846	143-254	166-178	194-200	233-243	1-127	99-116	SPGGYTNFQY (SEQ ID NO: 3011)
074B16	1847	133-246	156-169	185-191	224-235	1-117	99-106	KGEGYTNFQY (SEQ ID NO: 2991)
074B17	1848	143-253	167-177	195-201	234-244	1-127	99-116	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C01	1849	143-253	166-179	195-201	234-244	1-127	99-116	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C02	1850	143-253	166-179	195-201	234-244	1-127	99-116	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C03	1851	143-253	166-179	195-201	234-244	1-127	99-116	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C04	1852	143-253	166-179	195-201	234-244	1-127	99-116	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C05	1853	143-253	166-179	195-201	234-244	1-127	99-116	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C06	1854	143-253	166-179	195-201	234-244	1-127	99-116	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C07	1855	143-253	166-179	195-201	234-244	1-127	99-116	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C08	1856	140-249	164-174	190-196	229-239	1-126	99-113	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C09	1857	141-254	167-177	193-199	232-242	1-125	99-114	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C10	1858	143-253	167-177	193-199	232-242	1-125	99-114	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C11	1859	143-253	167-177	193-199	232-242	1-125	99-114	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C12	1860	143-253	167-177	193-199	232-242	1-125	99-114	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C13	1861	143-253	167-177	193-199	232-242	1-125	99-114	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C14	1862	143-253	167-177	193-199	232-242	1-125	99-114	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C15	1863	143-253	167-177	193-199	232-242	1-125	99-114	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C16	1864	143-253	167-177	193-199	232-242	1-125	99-114	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C17	1865	143-253	167-177	193-199	232-242	1-125	99-114	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C18	1866	143-253	167-177	193-199	232-242	1-125	99-114	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C19	1867	143-253	167-177	193-199	232-242	1-125	99-114	GGYDILITGYTGGYGMV (SEQ ID NO: 2766)
075C20	1868	147-257	168-182	196-204	237-246	1-131	102-120	DSYDILITGYTGGYGMV (SEQ ID NO: 3052)

TABLE 1-continued

scFv	SEQ ID	AAs of VL	AAs of VH	AAs that Immunoselectively Bind to B220				AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
				VL CDR1	VL CDR2	VL CDR3	AAs of VH CDR1		
1866	00707C10	141-251	163-176	192-198	231-240	1-25	50-66	99-114	MEYDITLYGGYGEY (SEQ ID NO: 2179)
1867	00707C11	141-251	163-176	192-198	231-240	1-25	50-66	99-114	MEYDITLYGGYGEY (SEQ ID NO: 2179)
1871	00707D04	141-251	162-176	188-194	231-240	1-25	50-66	99-114	MEYDITLYGGYGEY (SEQ ID NO: 2179)
1872	00707D11	141-251	163-176	192-198	231-240	1-25	50-66	99-114	MEYDITLYGGYGEY (SEQ ID NO: 2179)
1873	00707D12	140-247	161-171	187-193	226-236	1-24	35-66	99-113	EMVDTLYGTDADFI (SEQ ID NO: 2046)
1874	00707D13	142-252	164-177	193-199	232-241	1-26	35-66	99-115	EMVDTLYGTYLNADY (SEQ ID NO: 2862)
1875	00707D18	142-252	164-177	193-199	232-241	1-26	35-66	99-115	EMVDTLYGTYLNADY (SEQ ID NO: 2862)
1876	00707D08	141-248	164-174	190-196	229-237	1-25	35-66	99-114	MEYDITLYGGYGEY (SEQ ID NO: 2179)
1877	00707D09	141-251	163-176	192-198	231-240	1-25	50-66	99-114	MEYDITLYGGYGEY (SEQ ID NO: 2179)
1878	00707D06	141-251	163-176	192-198	231-240	1-25	50-66	99-114	MEYDITLYGGYGEY (SEQ ID NO: 2179)
1879	00707D02	141-248	164-174	190-196	229-237	1-25	35-66	99-114	MEYDITLYGGYGEY (SEQ ID NO: 2179)
1880	00707D05	143-253	165-178	194-200	233-242	1-27	35-66	99-116	DSYGYVYDADFI (SEQ ID NO: 2094)
1881	00707D07	147-254	169-170	186-192	225-233	1-21	26-35	99-110	DSYGYVYDADFI (SEQ ID NO: 2184)
1882	00707D03	132-239	155-165	181-187	220-228	1-16	26-35	99-105	TGSGYNDALDI (SEQ ID NO: 2191)
1883	00707D02	136-243	159-169	185-191	224-232	1-20	26-35	99-109	DWDWDY (SEQ ID NO: 2193)
1884	00707D01	136-243	159-169	185-191	224-232	1-20	26-35	99-104	DWDWDY (SEQ ID NO: 2193)
1885	00909D03	136-247	159-172	186-194	227-236	1-20	26-35	99-104	EVLYD (SEQ ID NO: 2195)
1886	00707D05	130-240	152-165	181-187	220-229	1-14	26-35	99-103	EVLYD (SEQ ID NO: 2210)
1887	00707D07	134-241	157-167	183-189	222-230	1-11	26-35	99-107	WTSGGAADI (SEQ ID NO: 2205)
1888	00707D01	131-241	153-166	182-188	221-230	1-11	26-35	99-104	DWDWDY (SEQ ID NO: 2193)
1889	00707D06	134-241	157-167	183-189	222-230	1-11	26-35	99-107	EVLYD (SEQ ID NO: 2205)
1890	00707D02	136-243	159-169	185-191	224-232	1-20	26-35	99-109	EVLYD (SEQ ID NO: 2205)
1891	00808D01	138-249	161-177	188-195	228-231	1-12	35-66	99-111	WTSGGAADI (SEQ ID NO: 2206)
1892	00808D01	135-247	158-171	187-193	226-236	1-19	26-35	99-108	VHSTGGAADI (SEQ ID NO: 2207)
1893	00808D01	142-254	166-178	194-200	233-241	1-26	35-66	99-115	EVSYHYHGGYVADY (SEQ ID NO: 2201)
1894	00808D03	138-249	161-173	189-195	238-238	1-12	26-35	99-111	VGGAADADVADY (SEQ ID NO: 2197)
1895	00808D01	141-253	164-177	193-199	232-234	1-25	35-66	99-114	EGGADADVADY (SEQ ID NO: 2204)
1896	00808D01	136-243	161-172	188-194	227-234	1-20	26-35	99-109	EGGYGYGGYADY (SEQ ID NO: 2209)
1897	00808D02	136-243	161-172	188-194	227-234	1-20	26-35	99-109	EGGYGYGGYADY (SEQ ID NO: 2209)
1898	00808D01	131-240	153-166	181-187	220-229	1-15	26-35	99-103	DLGAGTYD (SEQ ID NO: 2195)
1899	00808B08	137-247	159-171	187-193	226-236	1-21	26-35	99-110	DLGAGTYD (SEQ ID NO: 2207)
1900									

TABLE 1-continued  
self the Immunospecificity Bind to B12c

Clone ID	sFv SEQ ID NO	AA's of VL	AA's of VL CDR1	AA's of VL CDR2	AA's of VL CDR3	AA's of VH	AA's of VH CDR1	AA's of VH CDR2	AA's of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
079A11	1915	135-242	138-168	184-190	223-231	1-19	26-35	50-66	99-108	GPSYTYMAV (SEQ ID NO: 3114)
079A12	1916	134-243	136-168	184-190	223-232	1-18	26-35	50-66	99-108	GPSYTYMAV (SEQ ID NO: 3115)
079B03	1917	130-246	135-169	180-192	225-232	1-20	26-35	50-66	99-109	GNYSYDAPI (SEQ ID NO: 3112)
079B04	1918	130-246	135-169	180-192	225-232	1-20	26-35	50-66	99-109	LLSDY (SEQ ID NO: 3168)
079B07	1919	130-246	135-169	180-192	225-232	1-20	26-35	50-66	99-111	DESGYFRYED (SEQ ID NO: 3193)
079B09	1920	139-246	162-172	188-194	227-235	1-123	26-35	50-66	99-112	WESDVYSGAED (SEQ ID NO: 3128)
079B10	1921	139-246	162-172	188-194	227-235	1-123	26-35	50-66	99-117	VTSYSSGGVYGYMDV (SEQ ID NO: 3145)
079C04	1922	132-239	153-166	189-195	232-240	1-128	26-35	50-66	99-113	AGGSSSSVSDY (SEQ ID NO: 3190)
079C05	1923	132-239	153-166	189-195	232-240	1-128	26-35	50-66	99-117	AGGSSSSVSDY (SEQ ID NO: 3225)
079C07	1924	137-244	158-168	184-190	223-233	1-21	26-35	50-66	99-110	GLDYVATGLDY (SEQ ID NO: 3176)
079C09	1925	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVRYDILTSYLAGLDN (SEQ ID NO: 2751)
079D02	1926	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-106	EWEGEAD (SEQ ID NO: 3178)
079D03	1927	133-247	157-167	183-189	222-232	1-117	26-35	50-66	99-110	YATSSWAEPD (SEQ ID NO: 3123)
079D06	1928	133-247	157-167	183-189	222-232	1-117	26-35	50-66	99-110	YATSSWAEPD (SEQ ID NO: 3190)
079D07	1929	136-243	157-167	185-190	222-232	1-120	26-35	50-66	99-103	LIHF (SEQ ID NO: 3161)
079D08	1930	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103	LIHF (SEQ ID NO: 3161)
079D09	1931	131-238	152-162	178-184	217-227	1-115	26-35	50-66	99-104	DGSRD (SEQ ID NO: 3108)
079D11	1932	134-241	157-167	183-189	222-233	1-118	26-35	50-66	99-107	EGVAAGEDY (SEQ ID NO: 3123)
079D16	1933	136-244	158-168	184-190	223-233	1-120	26-35	50-66	99-109	EKGRSRVFD (SEQ ID NO: 3093)
079D17	1934	136-244	158-168	184-190	223-233	1-120	26-35	50-66	99-110	EKGRSRVFD (SEQ ID NO: 3189)
079D18	1935	136-243	159-169	185-191	224-233	1-120	26-35	50-66	99-116	GHYVYSSVYPAED (SEQ ID NO: 3107)
079E12	1936	143-253	165-177	193-199	239-242	1-127	26-35	50-66	99-106	GHYVYSSVYPAED (SEQ ID NO: 3098)
079E14	1937	133-241	154-164	180-186	219-220	1-117	26-35	50-66	99-106	LPPLDYDGGMGSGDWLGP (SEQ ID NO: 3219)
079E15	1938	148-253	169-179	195-201	234-242	1-132	26-35	50-66	101-121	ESLLTEYCGSDCY (SEQ ID NO: 3115)
079E16	1939	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-109	NSAPSPSPMDV (SEQ ID NO: 3099)
079E17	1940	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-109	NSAPSPSPMDV (SEQ ID NO: 3099)
079F09	1941	130-237	151-161	177-183	212-226	1-110	26-35	50-66	99-109	NITPLAMGDF (SEQ ID NO: 3166)
079F10	1942	136-243	157-167	185-191	222-232	1-120	26-35	50-66	99-109	NITPLAMGDF (SEQ ID NO: 3166)
079F12	1943	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109	ADYSNDYMDV (SEQ ID NO: 3166)
079F13	1944	136-243	157-167	185-189	222-232	1-120	26-35	50-66	99-109	NITPLAMGDF (SEQ ID NO: 3166)
079G05	1945	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-108	PFLESYVMDV (SEQ ID NO: 3124)
079G06	1946	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-108	GNISGRTLDY (SEQ ID NO: 3158)
079H05	1947	136-243	157-167	185-189	222-232	1-118	26-35	50-66	99-107	NSAPSPSPMDV (SEQ ID NO: 3192)
079H06	1948	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-104	GWLDLD (SEQ ID NO: 3210)
080A01	1949	131-242	154-166	182-188	221-231	1-115	26-35	50-66	99-104	EHSSSDY (SEQ ID NO: 3111)
080A02	1950	133-245	156-169	185-191	224-234	1-127	26-35	50-66	99-106	EGEGGVNAPYEDY (SEQ ID NO: 3160)
080A03	1951	141-253	164-177	192-198	232-242	1-125	26-35	50-66	99-114	EAGSGSYHSEFEDY (SEQ ID NO: 3188)
080A07	1952	141-253	164-177	192-198	232-242	1-125	26-35	50-66	99-114	IGHWGYTDY (SEQ ID NO: 3173)
080A10	1953	141-253	164-177	192-198	232-242	1-125	26-35	50-66	99-114	IGHWGYTDY (SEQ ID NO: 3173)
080A14	1954	141-252	164-176	192-198	231-241	1-125	26-35	50-66	99-111	LGKNTYSSWLDY (SEQ ID NO: 3140)
080B02	1955	138-248	161-172	188-194	227-237	1-122	26-35	50-66	99-111	VYGVGSYSLGTDV (SEQ ID NO: 3096)
080B03	1956	138-249	161-173	189-195	228-238	1-122	26-35	50-66	99-110	LGVAARGAEDL (SEQ ID NO: 3206)
080B06	1957	137-249	161-173	189-195	228-238	1-121	26-35	50-66	102-115	AVRSGPYTMDV (SEQ ID NO: 3125)
080B08	1958	142-254	165-177	193-199	232-243	1-126	26-37	52-69	99-106	GRPLEDY (SEQ ID NO: 3141)
080B09	1959	142-254	165-177	193-199	232-243	1-126	26-37	52-69	99-106	GRPLEDY (SEQ ID NO: 3141)
080B08	1960	136-248	159-172	188-194	227-237	1-120	26-37	52-67	100-109	KQRKEHDY (SEQ ID NO: 3100)

TABLE 1-continued

[illegible]

TABLE 1—continued  
selects the Immunospecificity Bind to BL25

Clone ID	scFv SEQ ID NO	AA's of VL	AA's of VL CDR1	AA's of VL CDR2	AA's of VH	AA's of VH CDR1	AA's of VH CDR2	AA's of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
08L1A08	2007	130-240	152-164	180-186	219-229	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1A09	2008	134-241	151-163	181-187	220-230	1-18	26-35	50-66	GAGSWEFL (SEQ ID NO: 3188)
08L1A10	2009	133-243	155-168	184-190	223-232	1-17	26-35	50-66	GDRAED (SEQ ID NO: 3119)
08L1B01	2010	130-236	151-161	177-183	216-225	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1B04	2011	134-244	156-169	185-191	224-233	1-18	26-35	50-66	GNAGAFED (SEQ ID NO: 2211)
08L1B05	2012	133-243	155-168	184-190	223-232	1-17	26-35	50-66	GDRAED (SEQ ID NO: 3119)
08L1B06	2013	134-244	156-169	185-191	224-233	1-18	26-35	50-66	GNAGAFED (SEQ ID NO: 3119)
08L1B07	2014	136-243	157-167	182-189	222-231	1-20	26-35	50-66	RYALDY (SEQ ID NO: 3164)
08L1B08	2015	132-239	153-163	179-185	218-228	1-16	26-35	50-66	RYALDY (SEQ ID NO: 3164)
08L1B09	2016	130-240	152-164	180-186	219-229	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1B10	2017	130-237	153-163	179-185	218-226	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1B11	2018	132-239	153-163	179-185	218-228	1-16	26-35	50-66	GFALYKD (SEQ ID NO: 3169)
08L1B12	2019	130-237	153-163	179-185	218-226	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1C08	2020	130-237	153-163	179-185	218-226	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1D04	2021	135-243	156-166	182-188	221-231	1-19	26-35	50-66	EDLGGAFED (SEQ ID NO: 3103)
08L1D06	2022	132-239	153-163	179-185	218-228	1-16	26-35	50-66	GDVATDY (SEQ ID NO: 3147)
08L1D08	2023	132-239	153-163	179-185	218-228	1-16	26-35	50-66	GDVATDY (SEQ ID NO: 3147)
08L1D09	2024	130-238	152-162	178-184	217-227	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1D10	2025	134-244	156-169	185-191	224-233	1-18	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1D11	2026	130-237	153-163	179-185	218-226	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1D12	2027	130-237	153-163	179-185	218-226	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1E02	2028	130-237	153-163	179-185	218-226	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1E03	2029	130-240	152-164	180-186	219-229	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1E05	2030	130-240	152-164	180-186	219-229	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1E06	2031	134-241	155-165	181-187	220-230	1-18	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1E07	2032	132-239	153-163	179-185	218-228	1-16	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1E08	2033	142-249	163-173	180-195	228-238	1-26	26-35	50-66	GLAPYKAGAFED (SEQ ID NO: 3184)
08L1F01	2034	130-239	152-164	180-186	219-228	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1F04	2035	132-239	153-163	179-185	218-228	1-16	26-35	50-66	RLBKAR (SEQ ID NO: 3170)
08L1F05	2036	130-237	151-161	177-183	216-226	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1F06	2037	134-244	156-169	185-191	224-233	1-18	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1F07	2038	130-237	153-163	179-185	218-226	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1F11	2039	130-237	153-163	179-185	218-226	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1G01	2040	130-237	153-163	179-185	218-226	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1G04	2041	130-240	152-164	180-186	219-229	1-14	26-35	50-66	SRSPYDAED (SEQ ID NO: 3097)
08L1G06	2042	135-245	157-170	186-192	225-234	1-19	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1G10	2043	130-237	153-163	179-185	218-226	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1H01	2044	130-237	153-163	179-185	218-226	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1H02	2045	130-240	152-164	180-186	219-229	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L1H04	2046	135-242	156-166	182-188	221-231	1-19	26-35	50-66	SNWGGAFED (SEQ ID NO: 3302)
08L1H06	2047	130-240	152-164	180-186	219-229	1-14	26-35	50-66	LAED (SEQ ID NO: 3174)
08L1H08	2048	130-240	152-164	180-186	219-229	1-14	26-35	50-66	DTTDT (SEQ ID NO: 2203)
08L2A02	2049	139-249	161-173	181-195	228-238	1-23	26-35	50-66	PAASRGKDAED (SEQ ID NO: 3129)
08L2A03	2050	132-239	152-163	178-184	217-227	1-14	26-35	50-66	LSGDS (SEQ ID NO: 3122)
08L2A08	2051	134-243	157-167	182-189	222-231	1-20	26-35	50-66	RYALDY (SEQ ID NO: 3164)
08L2A11	2052	130-240	152-165	181-187	220-229	1-14	26-35	50-66	FVLVD (SEQ ID NO: 2210)

TABLE 1-continued  
scFvs that Immunorecognize Bist to B1-25

Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
08B3066	2053	131-238	154-164	180-186	219-227	1-115	26-35	50-66	99-104	GGKGVY (SEQ ID NO: 3135)
08B3067	2054	131-241	157-166	183-189	222-230	1-118	26-35	50-66	99-107	EGVAAGEDY (SEQ ID NO: 3123)
08B3068	2055	131-241	153-166	182-188	221-230	1-115	26-35	50-66	99-104	DLDVEDY (SEQ ID NO: 2208)
08B3069	2056	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109	DDVVVVDVADY (SEQ ID NO: 3143)
08B3070	2057	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109	KKGRGRVFDY (SEQ ID NO: 3093)
08B3071	2058	137-244	158-168	184-190	223-233	1-121	26-35	50-66	99-110	LNHNKLLDLY (SEQ ID NO: 3106)
08B3072	2059	130-240	152-166	181-187	220-229	1-114	26-35	50-66	99-107	KKGRGRVFDY (SEQ ID NO: 3105)
08B3073	2060	130-240	152-166	181-187	220-229	1-114	26-35	50-66	99-107	TWNTDYM (SEQ ID NO: 3127)
08B3074	2061	130-240	152-166	181-187	220-229	1-114	26-35	50-66	99-107	FLDY (SEQ ID NO: 3167)
08B3075	2062	139-246	162-172	188-194	227-235	1-123	26-35	50-66	99-112	VEVEDVGSADF (SEQ ID NO: 3128)
08B3076	2063	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109	GGDMVTITDY (SEQ ID NO: 3177)
08B3077	2064	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109	ADVSDVYMDY (SEQ ID NO: 3166)
08B3078	2065	134-249	160-173	189-195	228-238	1-118	26-35	50-66	99-107	KKGRGRVFDY (SEQ ID NO: 3105)
08B3079	2066	135-250	161-174	190-196	229-239	1-122	26-35	50-66	99-110	GGKGVY (SEQ ID NO: 3135)
08B3080	2067	135-250	161-174	190-196	229-239	1-122	26-35	50-66	99-110	GGKGVY (SEQ ID NO: 3135)
08B3081	2068	139-246	160-170	189-195	228-237	1-116	26-35	50-66	99-109	GNADAFDI (SEQ ID NO: 3223)
08B3082	2069	136-243	159-169	185-191	224-233	1-123	26-35	50-66	99-112	PAASSRGKDFDI (SEQ ID NO: 3129)
08B3083	2070	137-248	160-172	188-194	227-237	1-121	26-35	50-66	99-109	DSRPTNRAFDY (SEQ ID NO: 3110)
08B3084	2071	135-248	158-171	187-193	226-237	1-119	26-35	50-66	101-110	LHGTGSGCF (SEQ ID NO: 3146)
08B3085	2072	137-247	160-173	189-195	228-238	1-118	26-35	50-66	99-107	KKGRGRVFDY (SEQ ID NO: 3105)
08B3086	2073	137-247	160-173	189-195	228-238	1-118	26-35	50-66	99-107	KKGRGRVFDY (SEQ ID NO: 3105)
08B3087	2074	138-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111	VYDVTYEMGADI (SEQ ID NO: 3172)
08B3088	2075	137-248	162-172	188-194	227-235	1-121	26-35	50-66	99-111	DLAAAGDAFDI (SEQ ID NO: 3194)
08B3089	2076	135-247	158-171	187-193	226-236	1-119	26-35	50-66	99-110	DLKNGVALEDS (SEQ ID NO: 3197)
08B3090	2077	135-246	158-171	187-193	226-235	1-119	26-35	50-66	99-108	DEVSLIMDY (SEQ ID NO: 3201)
08B3091	2078	136-249	159-172	188-194	227-237	1-120	26-35	50-66	99-108	FGAGLLIDY (SEQ ID NO: 3195)
08B3092	2079	136-249	159-172	188-194	227-237	1-120	26-35	50-66	99-108	FGAGLLIDY (SEQ ID NO: 3195)
08B3093	2080	145-255	168-181	197-203	236-245	1-129	26-35	50-66	99-108	DOGHETANDY (SEQ ID NO: 3207)
08B3094	2081	148-262	173-188	204-210	243-251	1-132	26-35	50-66	99-121	DFQVYRGVIANPNTYGMVDY (SEQ ID NO: 3133)
08B3095	2082	142-254	165-178	194-200	243-251	1-126	26-35	50-66	99-115	DADGLVGAETINWTFIS (SEQ ID NO: 3126)
08B3096	2083	146-258	169-181	197-203	236-247	1-130	26-37	52-69	102-109	ATKSYDLIRATYTHMDY (SEQ ID NO: 2746)
08B3097	2084	132-242	156-166	182-188	221-231	1-116	26-35	50-66	99-111	VYDVTYEMGADI (SEQ ID NO: 3172)
08B3098	2085	135-249	160-174	190-196	229-239	1-122	26-35	50-66	99-111	VYDVTYEMGADI (SEQ ID NO: 3172)
08B3099	2086	135-249	160-174	190-196	229-239	1-122	26-35	50-66	99-111	VYDVTYEMGADI (SEQ ID NO: 3172)
08B3100	2087	143-255	166-179	195-201	226-234	1-119	26-35	50-66	99-108	DEPNDAFDY (SEQ ID NO: 3105)
08B3101	2088	134-245	162-172	188-194	227-235	1-122	26-35	50-66	99-116	DGDISDHNQYAMDY (SEQ ID NO: 3101)
08B3102	2089	138-248	165-177	186-192	225-234	1-118	26-35	50-66	99-111	EGTISENYSGMVDY (SEQ ID NO: 3209)
08B3103	2090	145-258	168-181	197-203	236-247	1-129	26-35	50-66	99-108	DYTHNAFDY (SEQ ID NO: 3127)
08B3104	2091	145-258	168-181	197-203	236-247	1-129	26-35	50-66	99-108	DYTHNAFDY (SEQ ID NO: 3127)
08B3105	2092	134-249	160-174	190-196	229-239	1-122	26-35	50-66	99-107	STLFGVGAEDY (SEQ ID NO: 3199)
08B3106	2093	136-249	161-174	190-196	229-239	1-122	26-35	50-66	99-111	SDWGVAFDI (SEQ ID NO: 3198)
08B3107	2094	136-249	161-174	190-196	229-239	1-122	26-35	50-66	99-109	ELVAGPGDFD (SEQ ID NO: 3148)
08B3108	2095	138-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111	VYDVTYEMGADI (SEQ ID NO: 3172)
08B3109	2096	137-249	161-174	189-195	228-238	1-121	26-35	50-66	101-110	SVAGRGHFDY (SEQ ID NO: 3089)
08B3110	2097	138-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111	GGKGVY (SEQ ID NO: 3135)
08B3111	2098	141-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114	EGGDAYDAVYFDY (SEQ ID NO: 2204)



TABLE 1-continued  
gene has Immunoreactivity Biot in BLIS

Clone ID	ncFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
D8SG09	2099	130-242	154-166	182-188	221-231	1-114	26-35	50-66	99-103	DPEDY (SEQ ID NO: 3134)
D8SG11	2100	140-252	161-176	192-198	231-241	1-114	26-35	50-66	99-113	ALLGLPSDFSYVDV (SEQ ID NO: 3139)
D8SH04	2101	131-243	155-167	183-189	222-232	1-125	26-35	50-66	99-114	EGEGGYNNAYFYDV (SEQ ID NO: 3160)
D8SH07	2103	133-245	157-167	183-189	222-232	1-117	26-35	50-66	99-106	TDYGGFDY (SEQ ID NO: 3092)
D8SH07	2105	137-247	161-171	187-193	226-236	1-121	26-35	50-66	99-110	GGVDISGVGFDP (SEQ ID NO: 3162)
D8SA03	2104	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-101	DTTDDY (SEQ ID NO: 2203)
D8SA08	2105	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-104	PLDGLGAFDI (SEQ ID NO: 3163)
D8AB08	2106	135-242	156-166	182-188	221-231	1-120	26-35	50-66	99-108	ESLGFSDAFDI (SEQ ID NO: 3116)
D8AC02	2107	136-243	157-167	183-189	222-232	1-114	26-35	50-66	99-109	SPLHSDAFDI (SEQ ID NO: 3120)
D8AD03	2108	137-244	158-168	184-190	223-233	1-120	26-35	50-66	99-103	DTTDDY (SEQ ID NO: 2203)
D8AD03	2109	133-243	155-168	184-190	223-232	1-117	26-35	50-66	99-106	EVGGAFDI (SEQ ID NO: 3157)
D8AE01	2110	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTDDY (SEQ ID NO: 2203)
D8AE06	2111	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTDDY (SEQ ID NO: 2203)
D8AE10	2112	130-237	151-161	177-183	216-226	1-114	26-35	50-66	99-103	DTTDDY (SEQ ID NO: 2203)
D8AE12	2113	130-240	152-164	180-186	217-227	1-114	26-35	50-66	99-103	DTTDDY (SEQ ID NO: 2203)
D8AF04	2114	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTDDY (SEQ ID NO: 2203)
D8AF04	2115	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTDDY (SEQ ID NO: 2203)
D8AF12	2116	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-103	DTTDDY (SEQ ID NO: 2203)
D8AF12	2117	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-108	ESLGFDAFDI (SEQ ID NO: 3116)
D8AH02	2118	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTDDY (SEQ ID NO: 2203)
D8AH02	2119	145-256	168-180	196-202	238-248	1-120	26-35	50-66	99-118	GARYDNRSHLSKYWFDL (SEQ ID NO: 3149)
D8AG09	2120	138-248	162-172	188-194	228-238	1-122	26-35	50-66	99-111	VGRKAAVDNTEY (SEQ ID NO: 3197)
D8AG09	2121	138-248	162-172	188-194	228-238	1-122	26-35	50-66	99-111	LGKNTSSWSLDY (SEQ ID NO: 3181)
D8AH06	2122	138-249	161-173	189-195	238-238	1-122	26-35	50-66	99-111	VGRKAAVDNTEY (SEQ ID NO: 3197)
D8AH06	2123	144-255	167-179	195-201	234-244	1-128	26-35	50-66	99-117	GGRTGTGTFGAFDI (SEQ ID NO: 3226)
I100A01	2124	136-247	158-172	188-194	227-236	1-120	26-35	50-66	99-117	VRQADPPRSFDP (SEQ ID NO: 3198)
I100A10	2125	140-251	163-175	191-197	227-236	1-120	26-35	50-66	99-113	VRQADPPRSFDP (SEQ ID NO: 3144)
I100B03	2126	136-247	158-172	188-194	227-236	1-120	26-35	50-66	99-109	DNGGGTIGTDY (SEQ ID NO: 3195)
I100C03	2127	136-247	158-172	188-194	227-236	1-120	26-35	50-66	99-109	DNGGGTIGTDY (SEQ ID NO: 3195)
I100C03	2128	140-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	VRQADPPRSFDP (SEQ ID NO: 3144)

## SEQUENCE LISTING

The patent contains a lengthy "Sequence Listing" section. A copy of the "Sequence Listing" is available in electronic form from the USPTO web site (<http://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US07138501B2>). An electronic copy of the "Sequence Listing" will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

What is claimed is:

1. An isolated antibody that immunospecifically binds B Lymphocyte Stimulator protein wherein said antibody comprises a first amino acid sequence at least 85% identical to amino acid residues 1-123 of SEQ ID NO:327 and a second amino acid sequence at least 85% identical to amino acid residues 141-249 of SEQ ID NO:327 and wherein said B Lymphocyte Stimulator protein is selected from the group consisting of:
  - (a) a protein whose amino acid sequence consists of amino acid residues 1-285 of SEQ ID NO:3228;
  - (b) a protein whose amino acid sequence consists of amino acid residues 134-285 of SEQ ID NO:3228; and
  - (c) a trimer of the protein of (b).
2. The antibody of claim 1 wherein the first amino acid sequence is at least 95% identical to amino acid residues 1-123 of SEQ ID NO:327 and the second amino acid sequence is at least 95% identical to amino acid residues 141-249 of SEQ ID NO:327.
3. The antibody of claim 1 wherein the amino acid differences between the first amino acid sequence and amino acid residues 1-123 of SEQ ID NO:327 are in one or more of the CDR regions located at amino acid residues 26-35, 50-66 and 99-112 of SEQ ID NO: 327 and wherein the amino acid differences between the second amino acid sequence and amino acid residues 141-249 of SEQ ID NO: 327 are in one or more of the CDR regions located at amino acid residues 163-173, 189-195 and 228-238 of SEQ ID NO: 327.
4. An isolated antibody that immunospecifically binds B Lymphocyte Stimulator protein wherein said antibody comprises amino acid residues 1-123 of SEQ ID NO: 327 and amino acid residues 141-249 of SEQ ID NO: 327 and wherein said B Lymphocyte Stimulator protein is selected from the group consisting of:
  - (a) a protein whose amino acid sequence consists of amino acid residues 1-285 of SEQ ID NO:3228;
  - (b) a protein whose amino acid sequence consists of amino acid residues 134-285 of SEQ ID NO:3228; and
  - (c) a trimer of the protein of (b).
5. The antibody of claim 1 wherein the antibody is selected from the group consisting of:
  - (a) a whole immunoglobulin molecule;
  - (b) an scFv;
  - (c) a chimeric antibody;
  - (d) a Fab fragment;
  - (e) an Fab' fragment; and
  - (f) an F(ab')<sub>2</sub>.
6. The antibody of claim 1 wherein the antibody is a monoclonal antibody.
7. The antibody of claim 1 wherein the antibody is a human antibody.
8. The antibody of claim 1 which comprises a heavy chain immunoglobulin constant domain selected from the group consisting of:
  - (a) a human IgM constant domain;
  - (b) a human IgG1 constant domain;
  - (c) a human IgG2 constant domain;
  - (d) a human IgG3 constant domain;
  - (e) a human IgG4 constant domain; and
  - (f) a human IgA constant domain.
9. The antibody of claim 1 which comprises a light chain immunoglobulin constant domain selected from the group consisting of:
  - (a) a human kappa constant domain; and
  - (b) a human lambda constant domain.
10. The antibody of claim 1 wherein the antibody has a dissociation constant ( $K_D$ ) less than or equal to  $10^{-9}$ M.
11. The antibody of claim 1 wherein the antibody is coupled to a detectable label.
12. The antibody of claim 11 wherein the detectable label is a radioisotope, an enzyme, a fluorescent label, a luminescent label, bioluminescent label or biotin.
13. The antibody of claim 12 wherein the radioisotope is <sup>125</sup>I, <sup>131</sup>I, <sup>111</sup>In, <sup>90</sup>Y, <sup>90m</sup>Tc, <sup>177</sup>Lu, <sup>166</sup>Ho, or <sup>152</sup>Sm.
14. The antibody of claim 1 wherein the antibody neutralizes said protein.
15. The antibody of claim 14 wherein the antibody diminishes the ability of said protein to bind to a receptor of said protein.
16. The antibody of claim 15 wherein the receptor is TACI.
17. The antibody of claim 15 wherein the receptor is BCMA.
18. The antibody of claim 14 wherein the antibody diminishes the ability of said protein to stimulate B cell proliferation.
19. The antibody of claim 14 wherein the antibody diminishes the ability of said protein to stimulate immunoglobulin secretion by B cells.
20. The antibody of claim 4 wherein the antibody is selected from the group consisting of:
  - (a) a whole immunoglobulin molecule;
  - (b) an scFv;
  - (c) a chimeric antibody;
  - (d) a Fab fragment;
  - (e) an Fab' fragment; and
  - (f) an F(ab')<sub>2</sub>.
21. The antibody of claim 4 wherein the antibody is a monoclonal antibody.
22. The antibody of claim 4 wherein the antibody is a human antibody.
23. The antibody of claim 4 which comprises a heavy chain immunoglobulin constant domain selected from the group consisting of:

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- (a) a human IgM constant domain;
- (b) a human IgG1 constant domain;
- (c) a human IgG2 constant domain;
- (d) a human IgG3 constant domain;
- (e) a human IgG4 constant domain; and
- (f) a human IgA constant domain.

24. The antibody of claim 4 which comprises a light chain immunoglobulin constant domain selected from the group consisting of:

- (a) a human kappa constant domain; and
- (b) a human lambda constant domain.

25. The antibody of claim 4 wherein the antibody is coupled to a detectable label.

26. The antibody of claim 25 wherein the detectable label is a radioisotope, an enzyme, a fluorescent label, a luminescent label, bioluminescent label or biotin.

27. The antibody of claim 26 wherein the radioisotope is  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$ ,  $^{90}\text{Y}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{177}\text{Lu}$ ,  $^{166}\text{Ho}$ , or  $^{153}\text{Sm}$ .

28. An antibody purified from the cell line contained in American Type Culture Collection Deposit Number PTA-3239.

29. An antibody purified from the cell line contained in American Type Culture Collection Deposit Number PTA-3240.

30. The antibody of claim 4 which comprises a human IgG1 heavy chain immunoglobulin constant domain and a human lambda light chain immunoglobulin constant domain.

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31. The antibody of claim 4 wherein the antibody neutralizes said protein.

32. The antibody of claim 31 wherein the antibody diminishes the ability of said protein to bind to a receptor of said protein.

33. The antibody of claim 32 wherein the receptor is TACI.

34. The antibody of claim 32 wherein the receptor is BCMA.

35. The antibody of claim 31 wherein the antibody diminishes the ability of said protein to stimulate B cell proliferation.

36. The antibody of claim 31 wherein the antibody diminishes the ability of said protein to stimulate immunoglobulin secretion by B cells.

37. An isolated antibody that immunospecifically binds B Lymphocyte Stimulator protein wherein said antibody comprises amino acid residues 1-123 of SEQ ID NO:2 and amino acid residues 141-249 of SEQ ID NO:2 and wherein said B Lymphocyte Stimulator protein is selected from the group consisting of:

- (a) a protein whose amino acid sequence consists of amino acid residues 1-285 of SEQ ID NO:3228;
- (b) a protein whose amino acid sequence consists of amino acid residues 134-285 of SEQ ID NO:3228; and
- (c) a trimer of the protein of (b).

\* \* \* \* \*

U.S. Patent No. 7,138,501

Application for Patent Term Extension

# **Attachment E**

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 7,138,501 B2  
APPLICATION NO. : 09/880748  
DATED : November 21, 2006  
INVENTOR(S) : Ruben et al.

Page 1 of 52

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Title:

Delete "ANTIBODIES THAT IMMUNOSPECIICALLY BIND TO BLYS"  
and replace with --ANTIBODIES THAT IMMUNOSPECIFICALLY BIND TO B  
LYMPHOCYTE STIMULATOR PROTEIN--.

Title Page:

At INID (56) – Other Publications, delete "Kennell, D.E., Prog. Nucl. Acid Res.  
Med. Biol, 11:259:301 1971."

In the Specification:

Replace Table I, spanning pages 213-304 with the attached Table I.

Signed and Sealed this  
Sixth Day of March, 2007



JON W. DUDAS  
*Director of the United States Patent and Trademark Office*

Table 1: scFvs that Immunosepecifically Bind to B Lymphocyte Stimulator

Clone ID	seq SEQ ID NO	Abs at VL CDR1	Abs at VL CDR2	Abs at VL CDR3	Abs at VH CDR1	Abs at VH CDR2	Abs at VH CDR3	Abs at VH VH CDR Sequence (SEQ ID NO)
DOF025	1	138-248	160-179	189-195	228-227	1-122	26-35	50-66
DOF068	2	141-240	163-179	189-195	228-228	1-123	26-35	50-66
DOF041	3	144-234	166-179	195-201	224-243	1-123	26-37	50-66
DOF021	4	144-233	169-179	195-201	224-244	1-123	26-35	50-66
DOF021	5	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	6	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	7	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	8	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	9	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	10	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	11	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	12	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	13	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	14	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	15	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	16	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	17	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	18	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	19	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	20	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	21	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	22	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	23	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	24	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	25	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	26	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	27	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	28	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	29	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	30	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	31	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	32	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	33	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	34	145-239	169-179	195-201	224-244	1-125	26-35	50-66
DOF021	35	145-239	169-179	195-201	224-244	1-125	26-35	50-66

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1090D06	540	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFAPLDF (SEQ ID NO: 2467)
1090D07	541	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFPCTLDF (SEQ ID NO: 2468)
1090D08	542	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSSTLAF (SEQ ID NO: 2469)
1090D09	543	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFPRDPLAF (SEQ ID NO: 2470)
1090D12	544	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSPLAF (SEQ ID NO: 2471)
1090D13	545	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFPHAPLDF (SEQ ID NO: 2472)
1090D15	546	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2473)
1090D16	547	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2474)
1090D17	548	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2475)
1090D18	549	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2476)
1090D19	550	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2477)
1090D21	551	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2478)
1090D22	552	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2479)
1090D23	553	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2480)
1090D24	554	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2481)
1090D25	555	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2482)
1090D26	556	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2483)
1090D27	557	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2484)
1090D28	558	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2485)
1090D29	559	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2486)
1090D30	560	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2487)
1090D31	561	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2488)
1090D32	562	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2489)
1090D33	563	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2490)
1090D34	564	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2491)
1090D35	565	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2492)
1090D36	566	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2493)
1090D37	567	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2494)
1090D38	568	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2495)
1090D39	569	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2496)
1090D40	570	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2497)
1090D41	571	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2498)
1090D42	572	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2499)
1091A02	573	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2500)
1091A03	574	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2501)
1091A06	575	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2502)
1091A11	576	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2503)
1091B01	577	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2504)
1091B02	578	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2505)
1091B04	579	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2506)
1091B05	580	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2507)
1091B07	581	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRULLFFSAPLDF (SEQ ID NO: 2508)







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1001A10	876	141-241	165-176	194-198	211-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1001A12	877	141-241	165-172	188-194	237-237	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1001B02	878	141-241	159-171	197-198	226-236	1-121	26-35	50-66	99-114	DEHKTGTGMDY (SEQ ID NO: 2046)
1001B07	879	141-241	163-178	197-198	211-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1001C01	880	141-241	166-179	194-198	231-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1001C02	881	141-241	166-179	194-198	231-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1001C03	882	141-241	166-179	194-198	231-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1001C04	883	141-241	166-179	194-198	231-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1001D08	884	141-241	166-179	194-198	231-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1001E05	885	141-241	166-179	194-198	231-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1001F07	886	141-241	166-179	194-198	231-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1001G01	887	141-241	166-179	194-198	231-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1001H03	888	141-241	166-179	194-198	231-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1001I08	889	141-241	166-179	194-198	231-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1001J01	890	141-241	166-179	194-198	231-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1002A01	891	141-241	166-179	194-198	231-240	1-125	26-35	50-66	99-114	ATDPLTGTSDGTH (SEQ ID NO: 2153)
1002A06	892	142-249	163-173	199-198	231-240	1-124	26-34	49-63	98-113	ELGSSVGAATGALM (SEQ ID NO: 2852)
1002A07	893	141-246	163-173	199-198	231-240	1-124	26-34	49-63	98-113	ELGSSVGAATGALM (SEQ ID NO: 2852)
1002A08	894	141-246	163-173	199-198	231-240	1-124	26-34	49-63	98-113	ELGSSVGAATGALM (SEQ ID NO: 2852)
1002B03	895	140-246	163-173	199-198	231-240	1-124	26-34	49-63	98-113	ELGSSVGAATGALM (SEQ ID NO: 2852)
1002B09	896	142-249	163-173	199-198	231-240	1-124	26-34	49-63	98-113	ELGSSVGAATGALM (SEQ ID NO: 2852)
1003C01	897	142-252	164-175	198-198	231-241	1-124	26-34	49-63	98-113	ELGSSVGAATGALM (SEQ ID NO: 2852)
1003C02	898	142-252	164-175	198-198	231-241	1-124	26-34	49-63	98-113	ELGSSVGAATGALM (SEQ ID NO: 2852)
1003C03	899	142-250	164-174	198-198	229-239	1-123	26-33	50-65	99-114	ELGSSVGAATGALM (SEQ ID NO: 2852)
1003C04	900	142-250	164-174	198-198	229-239	1-123	26-33	50-65	99-114	ELGSSVGAATGALM (SEQ ID NO: 2852)
1003D05	901	140-246	164-174	198-198	229-239	1-123	26-33	50-65	99-114	ELGSSVGAATGALM (SEQ ID NO: 2852)
1003E03	902	141-253	164-175	198-198	231-242	1-125	26-35	50-65	99-114	ELGSSVGAATGALM (SEQ ID NO: 2852)
1003F01	903	141-253	163-175	198-198	231-242	1-124	26-34	49-63	98-113	ELGSSVGAATGALM (SEQ ID NO: 2852)
1003G02	904	140-251	163-175	198-198	231-242	1-124	26-34	49-63	98-113	ELGSSVGAATGALM (SEQ ID NO: 2852)
1003G03	905	143-254	163-175	198-198	231-242	1-124	26-34	49-63	98-113	ELGSSVGAATGALM (SEQ ID NO: 2852)
1003G04	906	143-254	163-175	198-198	231-242	1-124	26-34	49-63	98-113	ELGSSVGAATGALM (SEQ ID NO: 2852)
1004D05	907	144-255	168-181	197-203	236-243	1-129	26-35	50-66	99-116	DEHKTGTGMDY (SEQ ID NO: 2046)
1005011	908	144-251	165-175	194-197	230-240	1-128	26-35	50-66	99-116	DEHKTGTGMDY (SEQ ID NO: 2046)
1005B02	909	142-253	164-176	198-198	233-242	1-124	26-35	50-65	99-117	DEHKTGTGMDY (SEQ ID NO: 2046)
1005B05	910	141-251	163-176	198-198	231-240	1-124	26-34	49-63	98-113	ELGSSVGAATGALM (SEQ ID NO: 2852)
1005B06	911	143-249	163-173	198-198	228-238	1-126	26-36	50-66	99-115	DEHKTGTGMDY (SEQ ID NO: 2155)
1005B07	912	141-249	162-172	188-194	227-237	1-125	26-35	50-65	99-114	DEHKTGTGMDY (SEQ ID NO: 2155)
1005B08	913	141-249	162-172	188-194	227-237	1-125	26-35	50-65	99-114	DEHKTGTGMDY (SEQ ID NO: 2155)
1005B09	914	141-249	162-172	188-194	227-237	1-125	26-35	50-65	99-114	DEHKTGTGMDY (SEQ ID NO: 2155)
1005C01	915	137-247	159-172	188-194	227-235	1-121	26-35	50-65	98-110	TYMLTGTGMDY (SEQ ID NO: 2866)
1005C02	916	141-249	162-172	188-194	227-237	1-125	26-35	50-65	99-114	DEHKTGTGMDY (SEQ ID NO: 2155)
1005D02	917	141-251	163-176	195-198	231-240	1-125	26-35	50-65	99-114	DEHKTGTGMDY (SEQ ID NO: 2155)

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1005D09	918	143-249	163-175	191-197	230-238	1-126	26-35	50-66	99-115	GAYVHLYHYFYGMGV (SEQ ID NO: 2860)
1005E01	919	144-248	162-175	191-197	230-238	1-126	26-35	50-66	99-115	GTYVHLYHYFYGMGV (SEQ ID NO: 2774)
1005F00	920	141-248	162-172	188-194	229-237	1-125	26-35	50-65	99-114	SHYDLTGMYVYDL (SEQ ID NO: 2166)
1005F01	921	144-248	164-174	190-196	229-238	1-128	26-35	50-66	99-115	IQKDLTGYYGMGV (SEQ ID NO: 2021)
1005F02	922	144-248	164-174	190-196	229-238	1-128	26-35	50-66	99-115	YKQDLTGYYGMGV (SEQ ID NO: 2022)
1005F03	923	144-248	164-174	190-196	229-238	1-128	26-35	50-66	99-115	TYKDLTGYYGMGV (SEQ ID NO: 2023)
1005F04	924	146-247	166-171	187-193	226-236	1-124	26-35	50-66	99-113	TYKDLTGYYGMGV (SEQ ID NO: 2046)
1005F05	925	144-248	166-171	187-193	226-236	1-124	26-35	50-66	99-113	SYKDLTGYYGMGV (SEQ ID NO: 2850)
1005F06	926	144-248	166-171	187-193	226-236	1-124	26-35	50-66	99-114	DKRYDLTGYYGMGV (SEQ ID NO: 2859)
1005F07	927	145-249	165-175	191-197	229-238	1-126	26-35	50-66	99-115	QATYDLTGYYGMGV (SEQ ID NO: 2869)
1005F08	928	140-247	161-171	187-193	226-236	1-124	26-35	50-65	99-113	QATYDLTGYYGMGV (SEQ ID NO: 2860)
1005F09	929	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112	SGHLLFYGMGV (SEQ ID NO: 2857)
1005G00	930	143-249	165-177	191-199	233-242	1-127	26-35	50-66	99-116	GQYSSWLKGGPYNWEP (SEQ ID NO: 2697)
1005G01	931	143-249	165-177	191-199	233-242	1-127	26-35	50-66	99-116	GQYSSWLKGGPYNWEP (SEQ ID NO: 2697)
1005G02	932	142-248	164-176	190-198	232-241	1-127	26-35	50-66	99-114	ALRYDLTGYYGMGV (SEQ ID NO: 2863)
1005G03	933	142-248	164-176	190-198	232-241	1-127	26-35	50-66	99-114	ALRYDLTGYYGMGV (SEQ ID NO: 2863)
1005G04	934	142-248	164-176	190-198	232-241	1-127	26-35	50-66	99-114	SYKDLTGYYGMGV (SEQ ID NO: 2879)
1005G05	935	143-249	165-177	191-199	233-242	1-127	26-35	50-66	99-116	GQYSSWLKGGPYNWEP (SEQ ID NO: 2877)
1005G06	936	146-245	169-179	195-201	234-242	1-139	26-35	50-65	99-105	RGYDLTGYYGMGV (SEQ ID NO: 2820)
1005G07	937	132-239	163-173	179-185	218-228	1-116	26-35	50-65	99-106	DKGSLTGYYTHFYGMGV (SEQ ID NO: 2761)
1005G08	938	146-245	167-177	191-199	233-242	1-139	26-35	50-65	99-116	GQYSSWLKGGPYNWEP (SEQ ID NO: 2867)
1005H00	939	143-249	165-177	191-199	233-242	1-127	26-35	50-66	99-116	ATYDLTGYYGMGV (SEQ ID NO: 2155)
1005H01	940	141-251	163-175	190-198	232-241	1-125	26-35	50-66	99-114	ATYDLTGYYGMGV (SEQ ID NO: 2155)
1005H02	941	143-249	165-177	191-199	233-242	1-127	26-35	50-66	99-116	ATYDLTGYYGMGV (SEQ ID NO: 2155)
1005H03	942	144-248	166-178	192-200	234-243	1-128	26-35	50-66	99-117	ATYDLTGYYGMGV (SEQ ID NO: 2155)
1005H04	943	144-248	166-178	192-200	234-243	1-128	26-35	50-66	99-117	ATYDLTGYYGMGV (SEQ ID NO: 2155)
1005H05	944	141-251	163-175	190-198	232-241	1-125	26-35	50-66	99-114	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H06	945	143-249	165-177	191-199	233-242	1-127	26-35	50-66	99-116	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H07	946	140-247	162-173	188-195	228-238	1-126	26-35	50-65	99-115	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H08	947	140-247	162-173	188-195	228-238	1-126	26-35	50-65	99-115	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H09	948	140-247	161-171	187-195	228-236	1-124	26-35	50-66	99-113	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H10	949	144-251	165-178	192-200	234-243	1-128	26-35	50-66	99-117	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H11	950	141-251	163-175	190-198	232-241	1-125	26-35	50-66	99-114	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H12	951	141-251	163-175	190-198	232-241	1-125	26-35	50-66	99-114	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H13	952	141-251	163-175	190-198	232-241	1-125	26-35	50-66	99-114	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H14	953	141-251	163-175	190-198	232-241	1-125	26-35	50-66	99-114	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H15	954	143-249	165-178	192-200	234-243	1-128	26-35	50-66	99-117	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H16	955	141-251	163-175	190-198	232-241	1-125	26-35	50-66	99-114	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H17	956	142-252	164-177	191-199	233-241	1-126	26-35	50-65	99-115	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H18	957	143-249	165-178	192-200	234-243	1-128	26-35	50-66	99-117	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H19	958	143-249	165-178	192-200	234-243	1-128	26-35	50-66	99-117	ATYDLTGYYGMGV (SEQ ID NO: 2153)
1005H20	959	141-251	163-175	190-198	232-241	1-125	26-35	50-66	99-114	ATYDLTGYYGMGV (SEQ ID NO: 2153)



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0308011	1002	136-246	158-171	187-193	226-235	1-120	26-35	50-66	99-109	AYDLELTOLDY (SEQ ID NO: 2866)
0308012	1003	143-253	165-178	194-200	231-242	1-127	26-35	50-66	99-116	DQDLELTGYHGVADY (SEQ ID NO: 2867)
0308013	1004	141-248	164-174	196-199	229-237	1-125	26-35	50-66	99-114	DQDLELTGMYTGVADY (SEQ ID NO: 2868)
0308014	1005	141-251	165-176	197-200	231-240	1-123	26-35	50-66	99-111	ATPDTLGGYTGEDY (SEQ ID NO: 2163)
0308015	1006	141-250	165-174	196-200	231-244	1-125	26-35	50-66	99-113	ATPDTLGGYTGEDY (SEQ ID NO: 2163)
0308016	1007	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	DQDLELTGYHGVADY (SEQ ID NO: 2869)
0308017	1008	141-248	164-174	196-199	229-237	1-125	26-35	50-66	99-114	TKDLELTGYTGVADY (SEQ ID NO: 2870)
0308018	1009	141-249	163-175	197-199	230-238	1-124	26-34	49-65	98-113	ELGSLVGAATGALDM (SEQ ID NO: 2174)
0308019	1010	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSLVGAATGALDM (SEQ ID NO: 2174)
0308020	1011	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGSLVGAATGALDM (SEQ ID NO: 2174)
0308021	1012	143-253	165-178	194-200	233-244	1-126	26-35	50-66	99-115	TKDGLGVATGVADY (SEQ ID NO: 2871)
0308022	1013	143-253	165-178	194-200	233-244	1-126	26-35	50-66	99-115	TKDGLGVATGVADY (SEQ ID NO: 2871)
0308023	1014	142-250	164-174	196-199	230-239	1-124	26-34	49-65	98-113	ELGSLVGAATGALDM (SEQ ID NO: 2174)
0308024	1015	146-256	168-180	196-202	235-245	1-129	26-35	50-66	99-118	DGSGVGLGVATGVADY (SEQ ID NO: 2872)
0308025	1016	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGSLVGAATGALDM (SEQ ID NO: 2174)
0308026	1017	140-250	162-174	190-195	229-239	1-123	26-35	50-65	99-112	RYGDFPTTYTGVADY (SEQ ID NO: 2753)
0308027	1018	141-247	163-173	189-195	228-236	1-124	26-34	49-65	98-113	ELGSLVGAATGALDM (SEQ ID NO: 2174)
0308028	1019	141-249	163-175	189-195	228-238	1-124	26-34	49-65	98-113	ELGSLVGAATGALDM (SEQ ID NO: 2174)
0308029	1020	141-250	164-175	192-198	231-241	1-124	26-34	49-65	98-113	ELGSLVGAATGALDM (SEQ ID NO: 2174)
0308030	1021	144-252	164-176	192-198	231-241	1-124	26-35	50-66	99-112	RYGDFPTTYTGVADY (SEQ ID NO: 2753)
0308031	1022	141-250	163-175	189-195	228-239	1-123	26-35	50-66	99-112	RYGDFPTTYTGVADY (SEQ ID NO: 2753)
0308032	1023	140-251	162-175	191-197	229-240	1-123	26-35	50-66	99-113	ELGSLVGAATGALDM (SEQ ID NO: 2174)
0308033	1024	141-249	163-173	189-195	228-238	1-124	26-34	49-65	98-112	ELGSLVGAATGALDM (SEQ ID NO: 2174)
0308034	1025	148-259	170-182	196-204	237-248	1-131	26-35	50-66	99-120	SPFKVYDALTOUSSYHGVADY (SEQ ID NO: 2159)
0308035	1026	149-256	171-181	196-203	238-245	1-131	26-35	50-66	99-120	SPFKVYDALTOUSSYHGVADY (SEQ ID NO: 2159)
0308036	1027	149-256	171-181	196-203	238-245	1-131	26-35	50-66	99-120	SPFKVYDALTOUSSYHGVADY (SEQ ID NO: 2159)
0308037	1028	149-257	171-181	197-203	239-246	1-131	26-35	50-66	99-120	SPFKVYDALTOUSSYHGVADY (SEQ ID NO: 2159)
0308038	1029	148-258	170-182	196-204	237-247	1-131	26-35	50-66	99-120	SPFKVYDALTOUSSYHGVADY (SEQ ID NO: 2159)
0308039	1030	139-249	161-175	189-195	228-238	1-121	26-35	50-66	99-110	GYDSSAFARADY (SEQ ID NO: 2156)
0308040	1031	138-248	160-173	188-195	228-237	1-121	26-35	50-66	99-110	GYDSSAFARADY (SEQ ID NO: 2156)
0308041	1032	148-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120	SPFKVYDALTOUSSYHGVADY (SEQ ID NO: 2159)
0308042	1033	146-257	168-181	196-203	238-248	1-131	26-35	50-66	99-120	SPFKVYDALTOUSSYHGVADY (SEQ ID NO: 2159)
0308043	1034	146-257	168-181	196-203	238-248	1-131	26-35	50-66	99-120	SPFKVYDALTOUSSYHGVADY (SEQ ID NO: 2159)
0308044	1035	139-249	162-173	189-195	228-238	1-121	26-35	50-66	99-110	GYDSSAFARADY (SEQ ID NO: 2156)
0308045	1036	138-248	160-173	188-195	228-237	1-121	26-35	50-66	99-110	GYDSSAFARADY (SEQ ID NO: 2156)
0308046	1037	138-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110	GYDSSAFARADY (SEQ ID NO: 2156)
0308047	1038	143-253	165-178	194-200	233-247	1-121	26-35	50-66	99-110	ATTSQRKQYATFYGVADY (SEQ ID NO: 2151)
0308048	1039	147-250	170-183	201-207	240-249	1-129	26-35	50-66	99-118	GYDSSAFARADY (SEQ ID NO: 2156)
0308049	1040	138-248	160-173	188-194	227-237	1-121	26-35	50-66	99-110	GYDSSAFARADY (SEQ ID NO: 2156)
0308050	1041	148-256	170-182	196-203	237-247	1-131	26-35	50-66	99-120	SPFKVYDALTOUSSYHGVADY (SEQ ID NO: 2159)
0308051	1042	148-256	170-182	196-203	237-247	1-131	26-35	50-66	99-120	SPFKVYDALTOUSSYHGVADY (SEQ ID NO: 2159)
0308052	1043	148-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120	SPFKVYDALTOUSSYHGVADY (SEQ ID NO: 2159)

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1014A12	1044	140-253	165-178	194-209	231-240	253-262	1-127	24-33	48-54	97-116	100PDLTGVSEDEEN (SEQ ID NO: 2119)
1014B12	1045	142-254	167-179	195-210	232-241	254-263	1-128	25-34	49-55	98-117	100PDLTGVSEDEEN (SEQ ID NO: 2120)
1014C10	1046	141-251	166-178	194-208	231-240	253-262	1-125	26-35	50-56	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2121)
1014C12	1047	141-251	167-179	195-210	232-241	254-263	1-126	26-35	50-56	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2122)
1014D06	1048	140-252	166-176	193-209	231-241	253-264	1-124	26-34	49-65	98-113	100PDLTGVSEDEEN (SEQ ID NO: 2123)
1014E02	1049	143-251	169-176	196-204	234-240	256-263	1-125	26-37	52-67	100-114	100PDLTGVSEDEEN (SEQ ID NO: 2124)
1016A08	1050	144-251	168-175	195-207	233-240	255-263	1-128	26-35	50-66	99-117	100PDLTGVSEDEEN (SEQ ID NO: 2125)
1016A09	1051	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2126)
1016A12	1052	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2127)
1016B06	1053	140-252	166-176	193-209	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2128)
1016C03	1054	148-253	169-179	196-201	234-244	256-264	1-132	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2129)
1016C09	1055	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2130)
1016C11	1056	148-253	169-179	196-201	234-244	256-264	1-132	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2131)
1016C13	1057	141-253	168-176	195-208	233-240	255-263	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2132)
1016D04	1058	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2133)
1016E04	1059	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2134)
1016F06	1060	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2135)
1016G01	1061	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2136)
1016G06	1062	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2137)
1016G06	1063	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2138)
1016G12	1064	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2139)
1016G12	1065	148-253	169-179	196-201	234-244	256-264	1-132	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2140)
1016G12	1066	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2141)
1017A06	1067	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2142)
1017A07	1068	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2143)
1017A11	1069	140-253	166-175	193-207	232-242	255-263	1-124	25-34	49-65	98-113	100PDLTGVSEDEEN (SEQ ID NO: 2144)
1017B12	1070	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2145)
1017C03	1071	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2146)
1017C12	1072	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2147)
1017D01	1073	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2148)
1017D02	1074	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2149)
1018A04	1075	144-254	166-179	196-201	234-243	256-265	1-128	26-35	50-66	99-117	100PDLTGVSEDEEN (SEQ ID NO: 2150)
1018A05	1076	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2151)
1018A11	1077	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2152)
1018B02	1078	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2153)
1018B02	1079	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2154)
1018C04	1080	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2155)
1018D02	1081	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2156)
1018E06	1082	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2157)
1018E08	1083	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2158)
1018E08	1084	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2159)
1018E08	1085	141-251	167-176	194-208	231-240	253-262	1-125	26-35	50-66	99-114	100PDLTGVSEDEEN (SEQ ID NO: 2160)







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02320401	1461-2240	1664-1774	1919-1296	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320402	1461-2251	1663-1766	1920-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320403	1461-2262	1663-1776	1921-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320404	1461-2273	1663-1787	1922-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320405	1461-2284	1663-1798	1923-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320406	1461-2295	1663-1809	1924-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320407	1461-2306	1663-1820	1925-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320408	1461-2317	1663-1831	1926-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320409	1461-2328	1663-1842	1927-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320410	1461-2339	1663-1853	1928-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320411	1461-2350	1663-1864	1929-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320412	1461-2361	1663-1875	1930-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320413	1461-2372	1663-1886	1931-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320414	1461-2383	1663-1897	1932-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320415	1461-2394	1663-1908	1933-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320416	1461-2405	1663-1919	1934-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320417	1461-2416	1663-1930	1935-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320418	1461-2427	1663-1941	1936-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320419	1461-2438	1663-1952	1937-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320420	1461-2449	1663-1963	1938-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320421	1461-2460	1663-1974	1939-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320422	1461-2471	1663-1985	1940-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320423	1461-2482	1663-1996	1941-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320424	1461-2493	1663-2007	1942-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320425	1461-2504	1663-2018	1943-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320426	1461-2515	1663-2029	1944-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320427	1461-2526	1663-2040	1945-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320428	1461-2537	1663-2051	1946-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320429	1461-2548	1663-2062	1947-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320430	1461-2559	1663-2073	1948-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320431	1461-2570	1663-2084	1949-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320432	1461-2581	1663-2095	1950-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320433	1461-2592	1663-2106	1951-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320434	1461-2603	1663-2117	1952-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320435	1461-2614	1663-2128	1953-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320436	1461-2625	1663-2139	1954-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320437	1461-2636	1663-2150	1955-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320438	1461-2647	1663-2161	1956-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320439	1461-2658	1663-2172	1957-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320440	1461-2669	1663-2183	1958-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320441	1461-2680	1663-2194	1959-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320442	1461-2691	1663-2205	1960-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320443	1461-2702	1663-2216	1961-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320444	1461-2713	1663-2227	1962-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320445	1461-2724	1663-2238	1963-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320446	1461-2735	1663-2249	1964-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320447	1461-2746	1663-2260	1965-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320448	1461-2757	1663-2271	1966-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320449	1461-2768	1663-2282	1967-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320450	1461-2779	1663-2293	1968-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320451	1461-2790	1663-2304	1969-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320452	1461-2801	1663-2315	1970-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320453	1461-2812	1663-2326	1971-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320454	1461-2823	1663-2337	1972-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320455	1461-2834	1663-2348	1973-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320456	1461-2845	1663-2359	1974-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320457	1461-2856	1663-2370	1975-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320458	1461-2867	1663-2381	1976-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320459	1461-2878	1663-2392	1977-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320460	1461-2889	1663-2403	1978-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320461	1461-2900	1663-2414	1979-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320462	1461-2911	1663-2425	1980-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320463	1461-2922	1663-2436	1981-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320464	1461-2933	1663-2447	1982-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320465	1461-2944	1663-2458	1983-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320466	1461-2955	1663-2469	1984-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320467	1461-2966	1663-2480	1985-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320468	1461-2977	1663-2491	1986-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320469	1461-2988	1663-2502	1987-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320470	1461-2999	1663-2513	1988-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320471	1461-3010	1663-2524	1989-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320472	1461-3021	1663-2535	1990-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320473	1461-3032	1663-2546	1991-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320474	1461-3043	1663-2557	1992-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320475	1461-3054	1663-2568	1993-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320476	1461-3065	1663-2579	1994-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320477	1461-3076	1663-2590	1995-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320478	1461-3087	1663-2601	1996-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320479	1461-3098	1663-2612	1997-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320480	1461-3109	1663-2623	1998-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320481	1461-3120	1663-2634	1999-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320482	1461-3131	1663-2645	2000-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320483	1461-3142	1663-2656	2001-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320484	1461-3153	1663-2667	2002-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320485	1461-3164	1663-2678	2003-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320486	1461-3175	1663-2689	2004-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320487	1461-3186	1663-2700	2005-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320488	1461-3197	1663-2711	2006-1298	2259-2349	1-123	24-35	50-66	99-116	DAMTDLTGLVYTLAFDML (SEQ ID NO: 2888)
02320489	1461-3208	1663-2722	2007-1298	225					

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1030C19	1212	141-250	103-115	191-197	235-239	1-124	35-34	49-65	98-113	ELFISVQATTCALDM (SEQ ID NO: 2179)
1030C11	1215	140-251	106-117	189-195	235-239	1-124	35-34	49-65	98-113	KYDGFPTTYYTAMV (SEQ ID NO: 2179)
1030C10	1215	140-251	106-117	189-195	235-239	1-124	35-34	49-65	98-113	KYDGFPTTYYTAMV (SEQ ID NO: 2179)
1030D07	1215	141-249	106-117	189-195	235-239	1-127	26-35	50-66	99-106	KYDGFPTTYYTAMV (SEQ ID NO: 2179)
1030D12	1217	141-251	103-115	191-197	235-240	1-124	26-34	49-65	98-112	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030E02	1217	140-251	103-115	191-197	235-240	1-123	26-35	50-66	98-112	KYDGFPTTYYTAMV (SEQ ID NO: 2174)
1030E05	1218	142-252	104-116	192-198	235-241	1-124	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030E06	1218	142-251	104-116	192-198	235-241	1-124	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030E24	1220	143-253	105-117	194-197	239-240	1-124	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030E29	1221	143-252	105-117	194-197	239-240	1-124	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030E30	1222	140-250	104-116	192-198	235-239	1-123	26-35	50-66	99-112	KYDGFPTTYYTAMV (SEQ ID NO: 2174)
1030F02	1223	142-252	104-116	192-198	235-240	1-124	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030F03	1223	142-252	104-116	192-198	235-240	1-124	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030F06	1226	141-254	104-116	192-198	235-240	1-123	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030F08	1226	141-254	104-116	192-198	235-240	1-123	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030F09	1227	142-253	104-116	192-198	235-240	1-124	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030F11	1228	140-250	102-115	190-196	235-239	1-124	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030F13	1228	140-250	102-115	190-196	235-239	1-124	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030F14	1229	141-251	103-115	191-197	235-240	1-124	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030F16	1229	141-251	103-115	191-197	235-240	1-124	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030F07	1231	144-253	105-117	194-197	239-240	1-123	26-35	50-66	99-112	KYDGFPTTYYTAMV (SEQ ID NO: 2174)
1030G09	1232	142-253	106-117	195-198	239-240	1-124	26-34	49-65	98-112	KYDGFPTTYYTAMV (SEQ ID NO: 2174)
1030H08	1233	146-255	108-121	197-204	243-248	1-124	26-34	49-65	98-112	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030H10	1233	146-255	108-121	197-204	243-248	1-124	26-34	49-65	98-112	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030H11	1235	141-252	103-115	191-197	235-240	1-124	26-35	50-66	99-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1030H11	1235	141-252	103-115	191-197	235-240	1-124	26-35	50-66	99-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1031A01	1237	138-248	104-116	192-198	235-237	1-121	26-34	49-65	98-113	ELGSIQVQATTCALDM (SEQ ID NO: 2174)
1031A03	1238	143-253	107-119	195-202	240-245	1-121	26-35	50-66	99-114	OTYDSAAKAAH (SEQ ID NO: 2180)
1031A04	1238	143-253	107-119	195-202	240-245	1-121	26-35	50-66	99-114	OTYDSAAKAAH (SEQ ID NO: 2180)
1031A05	1239	143-253	107-119	195-202	240-245	1-121	26-35	50-66	99-114	OTYDSAAKAAH (SEQ ID NO: 2180)
1031A12	1240	147-257	109-121	197-203	243-249	1-131	26-35	50-66	99-119	GRBETDKVFPWQATTCATTTTAMV (SEQ ID NO: 2189)
1031B05	1241	137-246	109-121	197-203	243-249	1-130	26-35	50-66	99-119	GRBETDKVFPWQATTCATTTTAMV (SEQ ID NO: 2189)
1031B06	1242	143-253	109-121	197-203	243-249	1-130	26-35	50-66	99-119	GRBETDKVFPWQATTCATTTTAMV (SEQ ID NO: 2189)
1031B07	1243	140-250	108-120	196-202	242-248	1-126	26-35	50-66	99-119	GRBETDKVFPWQATTCATTTTAMV (SEQ ID NO: 2189)
1031B08	1244	140-250	108-120	196-202	242-248	1-126	26-35	50-66	99-119	GRBETDKVFPWQATTCATTTTAMV (SEQ ID NO: 2189)
1031B09	1245	146-258	110-122	198-205	243-249	1-131	26-35	50-66	99-120	SNPKWYTAALIGSTYTHAMV (SEQ ID NO: 2189)
1031B11	1246	138-244	109-121	197-203	243-249	1-131	26-35	50-66	99-120	SNPKWYTAALIGSTYTHAMV (SEQ ID NO: 2189)
1031B12	1247	148-259	120-132	198-204	247-247	1-131	26-35	50-66	99-120	SNPKWYTAALIGSTYTHAMV (SEQ ID NO: 2189)
1031C01	1248	138-248	109-121	197-203	243-249	1-131	26-35	50-66	99-120	SNPKWYTAALIGSTYTHAMV (SEQ ID NO: 2189)
1031C02	1248	138-248	109-121	197-203	243-249	1-131	26-35	50-66	99-120	SNPKWYTAALIGSTYTHAMV (SEQ ID NO: 2189)
1031C03	1248	138-248	109-121	197-203	243-249	1-131	26-35	50-66	99-120	SNPKWYTAALIGSTYTHAMV (SEQ ID NO: 2189)
1031C04	1250	140-250	109-121	197-203	243-249	1-131	26-35	50-66	99-120	SNPKWYTAALIGSTYTHAMV (SEQ ID NO: 2189)
1031C08	1251	150-260	111-123	199-205	248-249	1-131	26-35	50-66	99-120	SNPKWYTAALIGSTYTHAMV (SEQ ID NO: 2189)
1031C11	1252	150-260	111-123	199-205	248-249	1-131	26-35	50-66	99-120	SNPKWYTAALIGSTYTHAMV (SEQ ID NO: 2189)
1031C11	1252	146-257	107-118	197-203	243-246	1-121	26-35	50-66	99-110	GRBETDKVFPWQATTCATTTTAMV (SEQ ID NO: 2189)
1031D01	1253	146-256	108-120	196-202	243-245	1-120	26-35	50-66	99-118	AUTYQKQKATTCATTTTAMV (SEQ ID NO: 2189)

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0331D04	1254	138-248	160-172	188-164	227-227	1-121	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331D06	1248	148-258	160-172	188-164	227-247	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331D08	1250	158-268	160-172	188-164	227-247	1-121	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331D09	1257	139-247	167-181	197-203	236-246	1-128	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331D11	1258	140-245	167-181	197-203	236-246	1-121	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331D12	1259	146-254	178-181	194-200	233-243	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331E01	1260	148-258	170-182	198-204	237-247	1-128	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331E05	1261	149-257	171-181	197-203	236-246	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331E07	1262	148-259	170-182	198-204	237-248	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331E08	1263	148-259	170-182	198-204	237-248	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331E09	1264	148-259	170-182	198-204	237-248	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331E10	1265	148-258	170-182	198-204	237-247	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331E11	1266	138-248	160-172	188-194	237-247	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331F01	1267	138-248	160-172	188-194	237-237	1-121	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331F04	1268	139-247	167-181	197-193	236-236	1-119	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331F06	1269	137-247	159-171	187-193	236-236	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331F10	1270	148-259	170-182	199-205	238-248	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331F11	1271	148-255	167-179	195-201	234-244	1-128	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331F12	1272	138-249	160-172	188-194	237-237	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331G01	1273	138-249	160-172	188-194	237-237	1-121	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331G03	1274	148-258	170-182	198-204	237-247	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331G05	1275	148-259	170-182	199-205	238-248	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331G06	1276	148-258	170-182	198-204	237-247	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331G07	1277	149-259	171-183	199-205	238-248	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331G09	1278	148-263	170-183	199-209	244-252	1-131	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331G12	1279	146-256	168-180	196-202	234-246	1-128	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331H01	1280	144-254	166-178	194-200	234-244	1-128	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331H02	1281	143-245	165-178	194-200	233-244	1-128	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331H03	1282	148-260	170-183	199-205	238-249	1-126	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331H06	1283	145-257	167-179	195-201	234-246	1-128	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331H09	1284	145-255	167-179	195-201	234-244	1-128	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331H10	1285	144-256	166-179	195-201	234-245	1-127	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331H08	1286	136-246	158-170	189-192	225-233	1-119	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331A08	1287	144-254	166-179	195-201	234-244	1-128	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331B11	1288	144-254	166-179	195-201	234-244	1-128	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331C08	1289	142-249	165-179	195-201	234-244	1-128	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0331C02	1290	162-260	185-193	199-195	228-238	1-125	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0333D03	1291	138-245	161-171	187-193	226-234	1-122	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0333D03	1292	141-248	168-176	192-198	231-240	1-125	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0333D05	1293	141-248	162-172	188-194	237-237	1-125	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0333D11	1294	140-247	161-171	187-193	226-236	1-124	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)
0333D12	1295	140-247	168-179	195-201	234-243	1-128	26-35	50-66	GTSSAFRAED (SEQ ID NO: 2136)

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1033001	1296	161-173	189-195	224-235	1-123	26-35	50-66	99-112	DIABLAALADAPES (SEQ ID NO: 2794)
1033002	1297	141-251	192-195	231-260	1-123	26-35	50-66	99-114	ATHEPLTQTSQDRI (SEQ ID NO: 2795)
1033003	1298	143-253	193-199	232-262	1-123	26-35	50-66	99-110	ATHEPLTQTSQDRI (SEQ ID NO: 2796)
1033004	1299	145-255	194-200	233-263	1-123	26-35	50-66	99-112	ATHEPLTQTSQDRI (SEQ ID NO: 2797)
1033005	1300	138-246	186-192	225-235	1-123	26-35	50-66	99-115	EGADYDLYGNYLVADY (SEQ ID NO: 2802)
1033006	1301	144-252	195-201	234-245	1-123	26-35	50-66	99-112	EGADYDLYGNYLVADY (SEQ ID NO: 2803)
1033007	1302	144-254	166-179	195-201	1-123	26-35	50-66	99-118	QKVVYDILGTYVYGVADY (SEQ ID NO: 2767)
1033008	1303	134-241	155-166	181-187	1-123	26-35	50-66	99-117	EVNTDILGTYVYGVADY (SEQ ID NO: 2768)
1033009	1304	143-253	165-178	194-200	1-123	26-35	50-66	99-107	DIQDGDHS (SEQ ID NO: 2804)
1033010	1305	142-250	165-178	194-200	1-123	26-35	50-66	99-108	DIQDGDHS (SEQ ID NO: 2805)
1033011	1306	142-250	165-178	194-200	1-123	26-35	50-66	99-113	POVPLTQTSQDRI (SEQ ID NO: 2806)
1033012	1307	140-247	162-171	188-194	1-123	26-35	50-66	99-114	POVPLTQTSQDRI (SEQ ID NO: 2807)
1033013	1308	139-246	161-170	187-193	1-123	26-35	50-66	99-113	ATVPLTQTSQDRI (SEQ ID NO: 2813)
1033014	1309	141-251	163-175	193-199	1-123	26-35	50-66	99-112	SHDILLPHYGVADY (SEQ ID NO: 2813)
1033015	1310	144-251	163-175	193-199	1-123	26-35	50-66	99-114	SHDILLPHYGVADY (SEQ ID NO: 2814)
1033016	1311	144-251	163-175	193-199	1-123	26-35	50-66	99-115	SHDILLPHYGVADY (SEQ ID NO: 2815)
1033017	1312	141-248	161-172	189-195	1-123	26-35	50-66	99-114	LYDILLTQTSQDRI (SEQ ID NO: 2822)
1033018	1313	140-250	162-173	194-197	1-123	26-35	50-66	99-113	LYDILLTQTSQDRI (SEQ ID NO: 2823)
1033019	1314	135-246	158-171	187-193	1-123	26-35	50-66	99-109	QWMLPVADRI (SEQ ID NO: 2864)
1033020	1315	144-251	163-175	193-199	1-123	26-35	50-66	99-117	SHDILLTQTSQDRI (SEQ ID NO: 2829)
1033021	1316	144-251	163-175	193-199	1-123	26-35	50-66	99-118	SHDILLTQTSQDRI (SEQ ID NO: 2830)
1033022	1317	146-256	168-181	197-203	1-123	26-35	50-66	99-114	SHDILLTQTSQDRI (SEQ ID NO: 2831)
1033023	1318	146-256	168-181	197-203	1-123	26-35	50-66	99-119	SHDILLTQTSQDRI (SEQ ID NO: 2832)
1033024	1319	140-250	162-173	194-197	1-123	26-35	50-66	99-113	SHDILLTQTSQDRI (SEQ ID NO: 2833)
1033025	1320	144-251	163-175	193-199	1-123	26-35	50-66	99-117	SHDILLTQTSQDRI (SEQ ID NO: 2834)
1033026	1321	142-249	163-175	193-199	1-123	26-35	50-66	99-115	SHDILLTQTSQDRI (SEQ ID NO: 2835)
1033027	1322	140-247	162-171	188-194	1-123	26-35	50-66	99-114	SHDILLTQTSQDRI (SEQ ID NO: 2836)
1033028	1323	140-247	162-171	188-194	1-123	26-35	50-66	99-114	SHDILLTQTSQDRI (SEQ ID NO: 2837)
1033029	1324	136-246	158-171	187-193	1-123	26-35	50-66	99-109	SHDILLTQTSQDRI (SEQ ID NO: 2838)
1033030	1325	140-250	162-173	194-197	1-123	26-35	50-66	99-113	SHDILLTQTSQDRI (SEQ ID NO: 2839)
1033031	1326	142-252	164-177	193-199	1-123	26-35	50-66	99-115	SHDILLTQTSQDRI (SEQ ID NO: 2840)
1033032	1327	147-257	169-182	198-204	1-123	26-35	50-66	99-110	SHDILLTQTSQDRI (SEQ ID NO: 2841)
1033033	1328	140-247	162-171	188-194	1-123	26-35	50-66	99-113	SHDILLTQTSQDRI (SEQ ID NO: 2842)
1033034	1329	140-247	162-171	188-194	1-123	26-35	50-66	99-113	SHDILLTQTSQDRI (SEQ ID NO: 2843)
1033035	1330	140-247	161-171	187-193	1-123	26-35	50-66	99-113	SHDILLTQTSQDRI (SEQ ID NO: 2844)
1033036	1331	141-245	162-172	188-194	1-123	26-35	50-66	99-114	SHDILLTQTSQDRI (SEQ ID NO: 2845)
1033037	1332	141-251	163-176	194-200	1-123	26-35	50-66	99-114	SHDILLTQTSQDRI (SEQ ID NO: 2846)
1033038	1333	143-253	165-178	194-200	1-123	26-35	50-66	99-117	SHDILLTQTSQDRI (SEQ ID NO: 2847)
1033039	1334	143-253	165-178	194-200	1-123	26-35	50-66	99-117	SHDILLTQTSQDRI (SEQ ID NO: 2848)
1033040	1335	143-253	165-178	194-200	1-123	26-35	50-66	99-115	SHDILLTQTSQDRI (SEQ ID NO: 2849)
1033041	1336	143-253	165-178	194-200	1-123	26-35	50-66	99-114	SHDILLTQTSQDRI (SEQ ID NO: 2850)
1033042	1337	143-253	165-178	194-200	1-123	26-35	50-66	99-116	SHDILLTQTSQDRI (SEQ ID NO: 2851)



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1380	141-251	163-176	192-198	231-240	26-35	59-66	99-116	ATTBTLTQVSEAFED (SEQ ID NO: 2153)
1381	138-248	160-172	180-195	238-237	26-35	59-66	99-111	TYTDLTQVSEAFED (SEQ ID NO: 2178)
1382	137-247	159-172	180-194	237-236	26-35	59-66	99-110	GVYFDTQVSEAFED (SEQ ID NO: 2179)
1383	141-251	161-173	181-196	239-238	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2153)
1384	141-251	161-173	181-196	239-238	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1385	141-248	164-174	188-195	239-237	26-35	59-66	99-114	LVKTSVYFSTYADY (SEQ ID NO: 2153)
1386	141-248	162-172	188-194	237-237	26-35	59-66	99-114	LVKTSVYFSTYADY (SEQ ID NO: 2153)
1387	141-248	162-172	188-194	237-237	26-35	59-66	99-114	LVKTSVYFSTYADY (SEQ ID NO: 2153)
1388	141-248	162-172	188-194	237-237	26-35	59-66	99-114	LVKTSVYFSTYADY (SEQ ID NO: 2153)
1389	141-248	162-172	188-194	237-237	26-35	59-66	99-114	LVKTSVYFSTYADY (SEQ ID NO: 2153)
1390	141-241	163-176	195-198	231-240	26-35	59-66	99-114	ATVTSAGAGAGED (SEQ ID NO: 2178)
1391	133-240	164-164	186-186	219-225	26-35	59-66	99-116	SVKLEDS (SEQ ID NO: 2142)
1392	146-235	165-181	197-203	238-245	26-35	59-66	99-119	DRYTLDTQVSEAFED (SEQ ID NO: 2187)
1393	139-245	160-170	186-193	235-235	26-35	59-66	99-112	GVYFDTQVSEAFED (SEQ ID NO: 2179)
1394	141-251	161-173	181-196	239-238	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2153)
1395	141-251	161-173	181-196	239-238	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1396	141-251	161-173	181-196	239-238	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1397	141-251	161-173	181-196	239-238	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1398	144-234	166-179	195-201	234-243	26-35	59-66	99-114	ATVTSAGAGAGED (SEQ ID NO: 2153)
1399	142-253	165-175	194-200	233-242	26-35	59-66	99-117	GVYFDTQVSEAFED (SEQ ID NO: 2179)
1400	142-253	165-175	194-200	233-242	26-35	59-66	99-117	GVYFDTQVSEAFED (SEQ ID NO: 2179)
1401	142-253	165-175	194-200	233-242	26-35	59-66	99-117	GVYFDTQVSEAFED (SEQ ID NO: 2179)
1402	142-253	165-175	194-200	233-242	26-35	59-66	99-117	GVYFDTQVSEAFED (SEQ ID NO: 2179)
1403	135-246	160-173	189-195	238-238	26-35	59-66	99-111	GVYFDTQVSEAFED (SEQ ID NO: 2179)
1404	135-246	160-173	189-195	238-238	26-35	59-66	99-111	GVYFDTQVSEAFED (SEQ ID NO: 2179)
1405	133-243	159-180	194-202	235-244	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2153)
1406	141-251	161-173	181-196	239-238	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1407	145-252	167-180	196-202	235-244	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1408	141-251	161-173	181-196	239-238	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1409	146-256	168-178	197-203	235-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1410	146-256	168-178	197-203	235-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1411	140-251	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1412	144-254	166-176	195-201	234-243	26-35	59-66	99-113	GVYFDTQVSEAFED (SEQ ID NO: 2179)
1413	140-250	165-175	194-200	233-242	26-35	59-66	99-113	GVYFDTQVSEAFED (SEQ ID NO: 2179)
1414	140-250	165-175	194-200	233-242	26-35	59-66	99-113	GVYFDTQVSEAFED (SEQ ID NO: 2179)
1415	142-252	167-177	195-198	231-241	26-35	59-66	99-111	GVYFDTQVSEAFED (SEQ ID NO: 2179)
1416	141-245	164-174	188-194	237-237	26-35	59-66	99-114	LVKTSVYFSTYADY (SEQ ID NO: 2153)
1417	141-245	164-174	188-194	237-237	26-35	59-66	99-114	LVKTSVYFSTYADY (SEQ ID NO: 2153)
1418	143-253	166-176	196-202	235-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2153)
1419	143-253	166-176	196-202	235-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2153)
1420	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1421	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1422	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1423	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1424	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1425	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1426	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1427	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1428	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1429	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1430	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1431	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1432	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1433	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1434	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1435	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1436	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1437	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1438	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1439	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1440	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)
1441	140-250	165-175	194-200	233-242	26-35	59-66	99-115	ATVTSAGAGAGED (SEQ ID NO: 2170)

1421	1375-245	1379-189	1838-191	2304-224	1-119	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2161)
1422	1375-246	1379-190	1838-192	2304-225	1-120	26-35	50-66	AGSGLATYGVYD (SEQ ID NO: 2162)
1423	1375-247	1379-191	1838-193	2304-226	1-121	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2163)
1424	138-165	1383-158	221-221	221-221	1-119	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2164)
1425	138-166	1383-159	221-222	221-222	1-120	26-35	50-66	CONTHLTATGVYD (SEQ ID NO: 2165)
1426	138-167	1383-160	221-223	223-223	1-123	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2166)
1427	138-168	1383-161	221-224	223-224	1-128	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2167)
1428	138-169	1383-162	221-225	223-225	1-128	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2168)
1429	138-170	1383-163	221-226	226-226	1-131	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2169)
1430	138-171	1383-164	221-227	226-227	1-131	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2170)
1431	137-169	1379-189	1838-191	2304-224	1-119	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2171)
1432	143-252	1404-177	1893-199	232-241	1-126	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2172)
1433	143-253	1404-178	1894-200	233-242	1-127	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2173)
1434	143-254	1404-179	1895-201	234-243	1-127	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2174)
1435	143-255	1404-180	1896-202	235-244	1-127	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2175)
1436	143-256	1404-181	1897-203	236-245	1-127	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2176)
1437	143-257	1404-182	1898-204	237-246	1-127	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2177)
1438	143-258	1404-183	1899-205	238-247	1-127	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2178)
1439	143-259	1404-184	1900-206	239-248	1-127	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2179)
1440	143-260	1404-185	1901-207	240-249	1-127	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2180)
1441	143-261	1404-186	1902-208	241-250	1-127	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2181)
1442	143-262	1404-187	1903-209	242-251	1-127	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2182)
1443	137-207	1379-171	1873-193	226-226	1-121	26-35	50-66	AGSGLATYGVYD (SEQ ID NO: 2183)
1444	137-208	1379-172	1873-194	226-227	1-121	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2184)
1445	142-249	1406-173	1890-195	238-228	1-126	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2185)
1446	142-250	1406-174	1890-196	238-229	1-126	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2186)
1447	144-234	1406-175	1890-197	238-230	1-128	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2187)
1448	144-235	1406-176	1890-198	238-231	1-128	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2188)
1449	144-236	1406-177	1890-199	238-232	1-127	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2189)
1450	144-237	1406-178	1890-200	238-233	1-127	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2190)
1451	135-245	1359-181	1862-192	225-224	1-119	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2191)
1452	148-238	1471-184	2000-206	239-248	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2192)
1453	148-239	1471-185	2000-207	239-249	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2193)
1454	148-240	1471-186	2000-208	239-250	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2194)
1455	137-241	1391-174	1897-193	226-246	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2195)
1456	142-248	1406-174	1890-196	238-228	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2196)
1457	135-245	1359-181	1862-192	225-224	1-119	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2197)
1458	148-238	1471-184	2000-206	239-248	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2198)
1459	148-239	1471-185	2000-207	239-249	1-134	26-35	50-67	ONKDHGTOMYV (SEQ ID NO: 2199)
1460	140-250	1406-175	1890-197	238-230	1-128	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2200)
1461	140-251	1406-176	1890-198	238-231	1-128	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2201)
1462	140-252	1406-177	1890-199	238-232	1-127	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2202)
1463	146-256	1468-175	1890-198	238-231	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2203)
1464	146-257	1468-176	1890-199	238-232	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2204)
1465	146-258	1468-177	1890-200	238-233	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2205)
1466	146-259	1468-178	1890-201	238-234	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2206)
1467	146-260	1468-179	1890-202	238-235	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2207)
1468	146-261	1468-180	1890-203	238-236	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2208)
1469	146-262	1468-181	1890-204	238-237	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2209)
1470	146-263	1468-182	1890-205	238-238	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2210)
1471	146-264	1468-183	1890-206	238-239	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2211)
1472	146-265	1468-184	1890-207	238-240	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2212)
1473	146-266	1468-185	1890-208	238-241	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2213)
1474	146-267	1468-186	1890-209	238-242	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2214)
1475	146-268	1468-187	1890-210	238-243	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2215)
1476	146-269	1468-188	1890-211	238-244	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2216)
1477	146-270	1468-189	1890-212	238-245	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2217)
1478	146-271	1468-190	1890-213	238-246	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2218)
1479	146-272	1468-191	1890-214	238-247	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2219)
1480	146-273	1468-192	1890-215	238-248	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2220)
1481	135-245	1359-181	1862-192	225-224	1-119	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2161)
1482	148-238	1471-184	2000-206	239-248	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2162)
1483	148-239	1471-185	2000-207	239-249	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2163)
1484	148-240	1471-186	2000-208	239-250	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2164)
1485	137-241	1391-174	1897-193	226-246	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2165)
1486	142-248	1406-174	1890-196	238-228	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2166)
1487	135-245	1359-181	1862-192	225-224	1-119	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2167)
1488	148-238	1471-184	2000-206	239-248	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2168)
1489	148-239	1471-185	2000-207	239-249	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2169)
1490	148-240	1471-186	2000-208	239-250	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2170)
1491	137-241	1391-174	1897-193	226-246	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2171)
1492	142-248	1406-174	1890-196	238-228	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2172)
1493	135-245	1359-181	1862-192	225-224	1-119	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2173)
1494	148-238	1471-184	2000-206	239-248	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2174)
1495	148-239	1471-185	2000-207	239-249	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2175)
1496	148-240	1471-186	2000-208	239-250	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2176)
1497	137-241	1391-174	1897-193	226-246	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2177)
1498	142-248	1406-174	1890-196	238-228	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2178)
1499	135-245	1359-181	1862-192	225-224	1-119	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2179)
1500	148-238	1471-184	2000-206	239-248	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2180)
1501	148-239	1471-185	2000-207	239-249	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2181)
1502	148-240	1471-186	2000-208	239-250	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2182)
1503	137-241	1391-174	1897-193	226-246	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2183)
1504	142-248	1406-174	1890-196	238-228	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2184)
1505	135-245	1359-181	1862-192	225-224	1-119	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2185)
1506	148-238	1471-184	2000-206	239-248	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2186)
1507	148-239	1471-185	2000-207	239-249	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2187)
1508	148-240	1471-186	2000-208	239-250	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2188)
1509	137-241	1391-174	1897-193	226-246	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2189)
1510	142-248	1406-174	1890-196	238-228	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2190)
1511	135-245	1359-181	1862-192	225-224	1-119	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2191)
1512	148-238	1471-184	2000-206	239-248	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2192)
1513	148-239	1471-185	2000-207	239-249	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2193)
1514	148-240	1471-186	2000-208	239-250	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2194)
1515	137-241	1391-174	1897-193	226-246	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2195)
1516	142-248	1406-174	1890-196	238-228	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2196)
1517	135-245	1359-181	1862-192	225-224	1-119	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2197)
1518	148-238	1471-184	2000-206	239-248	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2198)
1519	148-239	1471-185	2000-207	239-249	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2199)
1520	148-240	1471-186	2000-208	239-250	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2200)
1521	137-241	1391-174	1897-193	226-246	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2201)
1522	142-248	1406-174	1890-196	238-228	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2202)
1523	135-245	1359-181	1862-192	225-224	1-119	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2203)
1524	148-238	1471-184	2000-206	239-248	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2204)
1525	148-239	1471-185	2000-207	239-249	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2205)
1526	148-240	1471-186	2000-208	239-250	1-133	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2206)
1527	137-241	1391-174	1897-193	226-246	1-124	26-35	50-66	ONKDHGTOMYV (SEQ ID NO: 2207)
1528	142-248	1406-174	1890-196	238-228	1-124	26		



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1644	135-245	127-100	185-191	226-234	1-119	26-35	59-66	99-108	QNGCEYDLYGADY (SEQ ID NO: 21661)
1645	135-245	127-100	185-191	226-234	1-119	26-35	59-66	99-108	GUSSONCEYADY (SEQ ID NO: 21661)
1646	135-245	127-100	185-191	226-234	1-121	26-35	59-66	99-108	QYVYVATDLYTGAGAGATY (SEQ ID NO: 28007)
1647	148-252	150-172	194-200	233-243	1-126	26-35	59-66	99-116	QYVYVATDLYTGAGATY (SEQ ID NO: 28007)
1648	148-252	150-172	194-200	233-243	1-126	26-35	59-66	99-116	HDYVYVATGATYTTG (SEQ ID NO: 27746)
1649	148-252	150-172	194-200	233-243	1-122	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1650	148-252	150-172	194-200	233-243	1-122	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1651	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1652	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1653	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1654	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1655	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1656	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1657	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1658	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1659	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1660	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1661	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1662	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1663	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1664	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1665	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1666	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1667	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1668	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1669	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1670	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1671	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1672	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1673	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1674	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116	QYVYVATGATYTTG (SEQ ID NO: 27746)
1675	148-247	161-177	187-193	226-236	1-124	26-35	59-66	99-116</	



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1076F08	1076F08	164-174	170-186	229-239	1-124	26-36	51-66	99-113	VYEDILTOYLAWEH (SEQ ID NO: 2709)
1076F09	1076F09	163-173	181-197	230-241	1-124	26-34	49-65	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2710)
1076F10	1076F10	162-184	190-211	231-244	1-124	26-34	49-65	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2711)
1076F11	1076F11	161-183	191-212	232-245	1-124	26-35	50-66	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2712)
1076F12	1076F12	160-182	195-220	233-246	1-127	26-35	50-66	99-116	GTEDILTOYNSAPQY (SEQ ID NO: 2800)
1076F13	1076F13	159-181	197-223	234-248	1-130	26-35	50-66	99-119	NOTVDELTOYVGYGAEV (SEQ ID NO: 2769)
1076F14	1076F14	163-173	194-197	239-240	1-124	26-35	50-66	99-113	ENYEDILTOYVYDY (SEQ ID NO: 2871)
1076F15	1076F15	165-175	191-197	239-240	1-125	26-35	50-66	99-114	THYEDILTOYSHEDY (SEQ ID NO: 2863)
1076F16	1076F16	163-175	191-197	239-240	1-124	26-34	49-65	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F17	1076F17	162-186	192-211	241-241	1-124	26-35	50-66	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2175)
1076F18	1076F18	161-185	193-212	242-242	1-124	26-35	50-66	99-114	ELGUSVGAATGALLM (SEQ ID NO: 2176)
1076F19	1076F19	160-186	195-201	234-245	1-127	26-35	50-66	99-116	OSQDILTOYVSHEDY (SEQ ID NO: 2265)
1076F20	1076F20	163-175	191-197	239-239	1-124	26-35	50-66	99-113	VYEDILTOYVSHEDY (SEQ ID NO: 2177)
1076F21	1076F21	165-175	191-197	239-239	1-124	26-35	50-66	99-113	VYEDILTOYVSHEDY (SEQ ID NO: 2177)
1076F22	1076F22	163-176	192-193	231-240	1-125	26-35	50-66	99-113	MEYEDILTOYGVYDY (SEQ ID NO: 2179)
1076F23	1076F23	164-174	190-196	239-239	1-125	26-35	50-66	99-114	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F24	1076F24	162-186	192-211	241-241	1-124	26-35	50-66	99-114	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F25	1076F25	161-185	193-212	242-242	1-124	26-35	50-66	99-114	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F26	1076F26	160-186	195-201	234-245	1-127	26-35	50-66	99-114	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F27	1076F27	163-175	191-197	239-239	1-125	26-35	50-66	99-114	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F28	1076F28	165-175	191-197	239-239	1-125	26-35	50-66	99-122	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F29	1076F29	164-176	192-193	231-240	1-125	26-35	50-66	99-106	ELGUSVGAATGALLM (SEQ ID NO: 2175)
1076F30	1076F30	163-176	192-193	231-240	1-125	26-35	50-66	99-106	ELGUSVGAATGALLM (SEQ ID NO: 2175)
1076F31	1076F31	162-184	190-196	239-239	1-125	26-35	50-66	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F32	1076F32	161-185	193-212	242-242	1-124	26-34	49-65	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F33	1076F33	160-186	195-201	234-245	1-127	26-34	49-65	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F34	1076F34	163-175	191-196	239-239	1-125	26-34	49-65	99-114	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F35	1076F35	165-175	191-196	239-239	1-125	26-34	49-65	99-114	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F36	1076F36	164-176	192-193	231-241	1-124	26-34	49-65	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F37	1076F37	163-176	192-193	231-241	1-124	26-35	50-66	99-120	DELSTILTOYVADYVOMED (SEQ ID NO: 2180)
1076F38	1076F38	162-186	192-211	241-241	1-124	26-35	50-66	99-117	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F39	1076F39	161-185	193-212	242-242	1-124	26-36	51-66	99-117	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F40	1076F40	160-186	195-201	234-245	1-127	26-35	50-66	99-120	TSQSVYEDILTOYVTHFYVYVOMED (SEQ ID NO: 2181)
1076F41	1076F41	163-175	191-197	239-239	1-125	26-35	50-66	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F42	1076F42	165-175	191-197	239-239	1-125	26-35	50-66	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F43	1076F43	164-176	192-193	231-240	1-125	26-35	50-66	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F44	1076F44	163-176	192-193	231-240	1-125	26-35	50-66	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F45	1076F45	162-186	192-211	241-241	1-124	26-35	50-66	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F46	1076F46	161-185	193-212	242-242	1-124	26-35	50-66	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F47	1076F47	160-186	195-201	234-245	1-127	26-35	50-66	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F48	1076F48	163-175	191-197	239-239	1-125	26-35	50-66	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F49	1076F49	165-175	191-197	239-239	1-125	26-35	50-66	99-113	ELGUSVGAATGALLM (SEQ ID NO: 2174)
1076F50	1076F50	164-176	192-193	231-240	1-125	26-35	50-66	99-114	ATUPMAGTSPGAEH (SEQ ID NO: 2183)
1076F51	1076F51	163-176	192-193	231-240	1-125	26-35	50-66	99-114	ATUPMAGTSPGAEH (SEQ ID NO: 2183)
1076F52	1076F52	162-186	192-211	241-241	1-125	26-35	50-66	99-114	SLATELLEMDY (SEQ ID NO: 2184)
1076F53	1076F53	161-185	193-212	242-242	1-125	26-35	50-66	99-109	SLATELLEMDY (SEQ ID NO: 2184)

1590	142-222	164-176	152-198	231-241	40-65	58-113	ELDSNGVATGALUDM (SEQ ID NO: 2147)
1591	141-231	163-175	151-197	230-240	41-64	59-112	ELDSNGVATGALUDM (SEQ ID NO: 2148)
1592	142-221	164-174	150-196	235-246	38-66	55-115	DHEDLITLTVALLAFEDY (SEQ ID NO: 2147)
1593	140-229	162-172	151-197	230-239	41-64	59-112	VYVYDILITLTVALLAFEDY (SEQ ID NO: 2147)
1594	144-231	163-175	151-197	230-240	38-66	55-117	DMQSYTDLITLTVALLAFEDY (SEQ ID NO: 2148)
1595	140-230	162-175	151-197	230-239	41-64	59-117	VYVYDILITLTVALLAFEDY (SEQ ID NO: 2147)
1596	150-257	171-181	159-208	236-246	38-66	55-123	HSNUTYTDLLITLTVALLAFEDY (SEQ ID NO: 2149)
1597	145-225	167-179	155-201	241-251	32-67	50-118	HSNUTYTDLLITLTVALLAFEDY (SEQ ID NO: 2149)
1598	146-226	168-180	156-202	242-252	33-66	51-119	HSNUTYTDLLITLTVALLAFEDY (SEQ ID NO: 2149)
1599	138-244	160-173	159-195	238-237	39-65	56-119	HSNUTYTDLLITLTVALLAFEDY (SEQ ID NO: 2149)
1600	144-226	166-180	156-202	235-245	39-66	56-119	DEYDILITLTVALLAFEDY (SEQ ID NO: 2149)
1601	140-230	162-175	151-197	230-239	38-66	55-113	DEYDILITLTVALLAFEDY (SEQ ID NO: 2149)
1602	143-223	165-178	154-200	233-242	41-64	58-116	DVYDILITLTVALLAFEDY (SEQ ID NO: 2153)
1603	148-235	171-181	157-203	236-244	32-69	102-121	DEYDILITLTVALLAFEDY (SEQ ID NO: 2153)
1604	146-236	168-181	157-203	236-245	31-69	99-119	DEYDILITLTVALLAFEDY (SEQ ID NO: 2153)
1605	141-231	163-175	151-198	231-240	38-66	55-114	REYDILITLTVALLAFEDY (SEQ ID NO: 2152)
1606	134-244	156-169	183-191	234-233	38-66	55-107	REYDILITLTVALLAFEDY (SEQ ID NO: 2152)
1607	146-226	168-180	156-202	241-251	32-67	100-119	REYDILITLTVALLAFEDY (SEQ ID NO: 2152)
1608	146-226	168-180	156-202	241-251	32-67	100-119	REYDILITLTVALLAFEDY (SEQ ID NO: 2152)
1609	141-248	162-172	188-194	227-227	39-66	99-114	ATYDILITLTVALLAFEDY (SEQ ID NO: 2153)
1610	147-253	163-177	193-203	236-246	34-66	99-120	ATYDILITLTVALLAFEDY (SEQ ID NO: 2153)
1611	143-253	163-177	193-199	232-242	41-62	94-116	ATYDILITLTVALLAFEDY (SEQ ID NO: 2153)
1612	142-252	164-177	193-199	232-241	41-62	94-115	GRYDILITLTVALLAFEDY (SEQ ID NO: 2158)
1613	140-230	162-175	191-197	230-239	38-66	55-113	GRYDILITLTVALLAFEDY (SEQ ID NO: 2158)
1614	135-243	155-167	183-191	227-232	31-66	99-106	GRYDILITLTVALLAFEDY (SEQ ID NO: 2158)
1615	138-243	155-167	183-191	227-232	31-66	99-106	GRYDILITLTVALLAFEDY (SEQ ID NO: 2158)
1616	140-250	162-175	191-197	224-234	38-66	99-111	INSQSYT (SEQ ID NO: 2159)
1617	140-250	162-175	191-197	224-234	38-66	99-111	INSQSYT (SEQ ID NO: 2159)
1618	140-250	162-175	191-197	224-234	38-66	99-111	INSQSYT (SEQ ID NO: 2159)
1619	143-251	165-178	194-200	233-242	32-67	100-116	SPQDYSQSYT (SEQ ID NO: 2159)
1620	142-249	163-173	193-195	230-239	38-66	99-111	SPQDYSQSYT (SEQ ID NO: 2159)
1621	149-256	170-180	196-202	235-245	30-66	99-122	SPQDYSQSYT (SEQ ID NO: 2159)
1622	141-248	162-172	188-194	227-237	31-66	99-114	ATYDILITLTVALLAFEDY (SEQ ID NO: 2153)
1623	141-248	162-172	188-194	227-237	31-66	99-114	ATYDILITLTVALLAFEDY (SEQ ID NO: 2153)
1624	141-248	162-172	188-194	227-237	31-66	99-114	ATYDILITLTVALLAFEDY (SEQ ID NO: 2153)
1625	144-254	166-179	193-201	234-243	30-66	99-117	WQYDILITLTVALLAFEDY (SEQ ID NO: 2158)
1626	145-255	167-180	194-202	235-244	30-66	99-118	WQYDILITLTVALLAFEDY (SEQ ID NO: 2158)
1627	142-252	164-177	193-199	232-242	39-66	99-119	WQYDILITLTVALLAFEDY (SEQ ID NO: 2158)
1628	142-252	164-177	193-199	232-242	39-66	99-119	WQYDILITLTVALLAFEDY (SEQ ID NO: 2158)
1629	139-249	161-174	190-195	229-234	31-66	99-113	EMADILITLTVALLAFEDY (SEQ ID NO: 2153)
1630	136-246	158-170	186-192	225-230	30-66	99-109	EMADILITLTVALLAFEDY (SEQ ID NO: 2153)
1631	141-253	163-177	191-197	229-242	31-66	99-114	ATYDILITLTVALLAFEDY (SEQ ID NO: 2153)



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1666F11	1074	1,02-232	164-177	153-169	232-241	1-126	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1666F12	1675	141-248	168-184	188-194	227-236	1-127	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1666G01	1676	143-248	155-168	184-194	223-232	1-127	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1666G02	1677	143-248	155-168	184-194	223-232	1-127	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1666G03	1678	133-242	155-166	182-188	231-231	1-119	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667A02	1679	141-248	162-172	188-194	227-236	1-125	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667A03	1680	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667A06	1681	141-248	162-172	188-194	227-236	1-123	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667A08	1682	137-247	159-171	187-193	226-236	1-124	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667A10	1683	140-250	163-175	191-197	230-239	1-124	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667B00	1684	142-253	164-172	193-199	232-242	1-126	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667B04	1685	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667B06	1686	134-244	159-172	188-194	227-236	1-121	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667C00	1687	141-248	159-172	188-194	227-236	1-121	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667C02	1688	141-248	163-176	192-198	231-240	1-125	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667C10	1689	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667C12	1690	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D01	1691	136-246	158-171	187-193	226-235	1-120	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D05	1692	137-244	158-168	184-190	223-233	1-121	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1693	146-255	168-180	196-202	235-245	1-130	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1694	137-244	158-168	184-190	223-233	1-121	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1695	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1696	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1697	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1698	142-252	164-176	192-198	231-241	1-126	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1699	144-256	166-179	195-201	234-243	1-128	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1700	141-248	164-174	193-195	229-227	1-123	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1701	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1702	139-246	160-178	186-192	223-233	1-123	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1703	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1704	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1705	140-258	163-176	192-198	231-240	1-124	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1706	141-251	163-176	192-198	231-240	1-124	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1707	141-251	163-176	192-198	231-240	1-124	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1708	141-251	163-176	192-198	231-240	1-124	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1709	143-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1710	143-254	170-183	199-203	238-246	1-131	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1711	135-247	163-176	192-198	226-236	1-117	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1712	141-251	163-176	192-198	231-240	1-124	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1713	142-252	164-176	192-198	231-241	1-125	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1714	137-245	159-169	185-191	224-234	1-119	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)
1667D06	1715	140-250	162-174	195-196	229-229	1-123	26-35	50-66	99-115	QATYLLTQYTFYGMVY (SEQ ID NO: 2660)

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0608311	1716	147-258	169-182	194-264	237-247	1-130	26-35	50-66	99-114	ESTRIBLTLVLVAAGDEV (SEQ ID NO: 3044)
0608309	1717	151-248	164-174	190-196	229-237	1-123	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2179)
0608308	1718	141-248	164-174	188-194	227-237	1-125	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2179)
0608307	1719	161-248	164-174	188-194	227-237	1-125	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2179)
0608306	1720	139-249	161-174	190-196	239-248	1-123	26-35	50-66	99-112	METDLITVYGGYDEV (SEQ ID NO: 2179)
0608312	1721	141-248	162-172	188-194	237-237	1-123	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2179)
0608306	1722	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	VLRITDLITGQNWDEF (SEQ ID NO: 3000)
0608309	1723	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	VLRITDLITGQNWDEF (SEQ ID NO: 3000)
0608309	1724	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	POTYDLITVYGGYDEV (SEQ ID NO: 2183)
0608309	1725	142-249	163-173	189-195	238-238	1-126	26-35	50-66	99-113	POTYDLITVYGGYDEV (SEQ ID NO: 2183)
0608311	1726	140-247	161-171	187-193	226-226	1-124	26-35	50-66	99-113	YTRITLITVYGGYDEV (SEQ ID NO: 2177)
0608305	1727	141-248	163-172	188-194	237-237	1-123	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2179)
0608312	1728	141-248	162-172	188-194	237-237	1-123	26-35	50-66	99-114	MYTDLITVYGGYDEV (SEQ ID NO: 2179)
0608312	1729	141-248	162-172	188-194	237-237	1-123	26-35	50-66	99-113	MYTDLITVYGGYDEV (SEQ ID NO: 2179)
0608306	1730	142-249	163-173	189-195	238-238	1-126	26-35	50-66	99-113	DRILYDLITVYGGYDEV (SEQ ID NO: 3039)
0608312	1731	145-252	166-176	192-198	231-241	1-129	26-35	50-66	99-118	DRILYDLITVYGGYDEV (SEQ ID NO: 3039)
0608311	1732	141-248	162-172	188-194	237-237	1-123	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2179)
0700403	1733	141-248	164-174	190-196	229-237	1-123	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2179)
0700403	1734	141-248	164-174	190-196	229-237	1-123	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2179)
0700801	1735	144-254	165-179	193-201	227-227	1-125	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2179)
0700803	1736	141-251	163-176	190-198	231-240	1-123	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2179)
0700803	1737	141-248	164-174	190-196	229-237	1-123	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2179)
0700204	1738	141-251	163-176	192-198	231-240	1-123	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2179)
0700204	1739	144-254	165-179	193-201	227-227	1-125	26-35	50-66	99-117	SQSDYDLITVYGGYDEV (SEQ ID NO: 3038)
0700204	1740	144-254	165-179	193-201	227-227	1-125	26-35	50-66	99-117	SQSDYDLITVYGGYDEV (SEQ ID NO: 3038)
0700204	1741	141-248	163-176	190-198	231-240	1-123	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2179)
0701A06	1742	135-245	156-166	182-183	221-221	1-119	26-35	50-66	99-114	METDLITVYGGYDEV (SEQ ID NO: 2161)
0701B02	1743	135-245	157-170	185-192	225-224	1-119	26-35	50-66	99-103	QAGDHYVGMDEV (SEQ ID NO: 2161)
0701B02	1744	137-247	158-172	186-194	227-226	1-121	26-35	50-66	99-110	QAGDHYVGMDEV (SEQ ID NO: 2161)
0701B02	1745	137-247	158-172	186-194	227-226	1-121	26-35	50-66	99-110	QAGDHYVGMDEV (SEQ ID NO: 2161)
0701D08	1746	137-247	158-172	186-194	227-226	1-121	26-35	50-66	99-110	QAGDHYVGMDEV (SEQ ID NO: 2161)
0701F01	1747	137-247	158-172	186-194	227-226	1-121	26-35	50-66	99-110	QAGDHYVGMDEV (SEQ ID NO: 2161)
0701G09	1748	141-251	163-176	192-198	231-240	1-123	26-35	50-66	99-114	ATTDLITVYGGYDEV (SEQ ID NO: 2183)
0702A01	1749	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-112	SKULLITVYGGYDEV (SEQ ID NO: 2183)
0702B02	1750	141-251	163-176	192-198	231-240	1-123	26-35	50-66	99-114	ATTDLITVYGGYDEV (SEQ ID NO: 2183)
0702B02	1751	137-247	159-172	188-194	227-226	1-121	26-35	50-66	99-110	ASSUMITVYGGYDEV (SEQ ID NO: 2161)
0702B10	1752	141-251	163-176	192-198	231-240	1-123	26-35	50-66	99-114	ASSUMITVYGGYDEV (SEQ ID NO: 2161)
0702B11	1753	140-249	162-173	189-195	228-228	1-124	26-35	50-66	99-113	ATTDLITVYGGYDEV (SEQ ID NO: 2183)
0702B12	1754	135-245	157-169	183-191	224-224	1-119	26-35	50-66	99-108	QAGDHYVGMDEV (SEQ ID NO: 2161)
0702C05	1755	135-245	157-169	183-191	224-224	1-119	26-35	50-66	99-114	ATTDLITVYGGYDEV (SEQ ID NO: 2183)
0702D01	1756	141-251	163-176	192-198	231-240	1-123	26-35	50-66	99-114	ATTDLITVYGGYDEV (SEQ ID NO: 2183)
0702D05	1757	133-245	157-169	183-191	224-224	1-119	26-35	50-66	99-108	QAGDHYVGMDEV (SEQ ID NO: 2161)





1880	141-211	163-176	192-198	231-240	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1881	141-211	163-176	192-198	231-240	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1882	141-211	163-176	192-198	231-240	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1883	141-211	163-176	192-198	231-240	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1884	140-259	162-175	191-197	230-239	1-124	26-35	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1885	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1886	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1887	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1888	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1889	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1890	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1891	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1892	140-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1893	143-253	165-178	194-200	233-242	1-127	26-35	89-116	ATYELTVOYSEBQ (SEQ ID NO: 215)
1894	143-253	165-178	194-200	233-242	1-127	26-35	89-116	ATYELTVOYSEBQ (SEQ ID NO: 215)
1895	135-245	157-169	188-194	224-237	1-119	26-35	89-108	ATYELTVOYSEBQ (SEQ ID NO: 215)
1896	141-248	163-172	188-194	224-237	1-123	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1897	146-269	163-178	195-199	228-238	1-126	26-35	89-116	ATYELTVOYSEBQ (SEQ ID NO: 215)
1898	139-246	160-170	189-192	229-235	1-123	26-35	89-112	ATYELTVOYSEBQ (SEQ ID NO: 215)
1899	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1900	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1901	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1902	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1903	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1904	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1905	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1906	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1907	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1908	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1909	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1910	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1911	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1912	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1913	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1914	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1915	143-253	165-178	194-200	233-242	1-127	26-35	89-116	ATYELTVOYSEBQ (SEQ ID NO: 215)
1916	143-253	165-178	194-200	233-242	1-127	26-35	89-116	ATYELTVOYSEBQ (SEQ ID NO: 215)
1917	135-245	157-169	188-194	224-237	1-119	26-35	89-108	ATYELTVOYSEBQ (SEQ ID NO: 215)
1918	141-248	163-172	188-194	224-237	1-123	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1919	146-269	163-178	195-199	228-238	1-126	26-35	89-116	ATYELTVOYSEBQ (SEQ ID NO: 215)
1920	139-246	160-170	189-192	229-235	1-123	26-35	89-112	ATYELTVOYSEBQ (SEQ ID NO: 215)
1921	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1922	145-255	167-179	193-199	232-244	1-129	26-35	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1923	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1924	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1925	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1926	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1927	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1928	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1929	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1930	141-251	163-175	191-197	230-239	1-125	26-35	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1931	140-251	162-175	191-197	230-239	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1932	141-251	163-175	191-197	230-239	1-125	26-34	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1933	143-253	165-178	194-200	233-242	1-127	26-34	89-116	ATYELTVOYSEBQ (SEQ ID NO: 215)
1934	143-253	165-178	194-200	233-242	1-127	26-34	89-116	ATYELTVOYSEBQ (SEQ ID NO: 215)
1935	135-245	157-169	188-194	224-237	1-119	26-34	89-108	ATYELTVOYSEBQ (SEQ ID NO: 215)
1936	141-248	163-172	188-194	224-237	1-123	26-34	89-114	ATYELTVOYSEBQ (SEQ ID NO: 215)
1937	146-269	163-178	195-199	228-238	1-126	26-34	89-116	ATYELTVOYSEBQ (SEQ ID NO: 215)
1938	139-246	160-170	189-192	229-235	1-123	26-34	89-112	ATYELTVOYSEBQ (SEQ ID NO: 215)
1939	145-255	167-179	193-199	232-244	1-129	26-34	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1940	145-255	167-179	193-199	232-244	1-129	26-34	89-118	ATYELTVOYSEBQ (SEQ ID NO: 215)
1941	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1942	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1943	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1944	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1945	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1946	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1947	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1948	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1949	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1950	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1951	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1952	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1953	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1954	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1955	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1956	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1957	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1958	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1959	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1960	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1961	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1962	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1963	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1964	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1965	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1966	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1967	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1968	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1969	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1970	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1971	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1972	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1973	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1974	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1975	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1976	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1977	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1978	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1979	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1980	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1981	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1982	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1983	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1984	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1985	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1986	141-251	163-175	191-197	230-240	1-124	26-34	89-113	ATYELTVOYSEBQ (SEQ ID NO: 215)
1987	141-251	163-175	191-197	230-240	1-124	26-34</		



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1874	137-262	154-167	183-189	272-281	1-119	26-35	59-66	99-104	DMWQV (SEQ ID NO: 2109)
1885	137-267	159-173	188-194	272-278	1-120	26-35	59-66	99-104	DMWQV (SEQ ID NO: 2109)
1886	139-240	155-165	181-187	220-229	1-114	26-35	59-66	99-104	FWLQV (SEQ ID NO: 2110)
1887	134-261	157-167	181-189	220-229	1-114	26-35	59-66	99-104	FWLQV (SEQ ID NO: 2110)
1888	137-261	153-166	182-188	221-230	1-115	26-35	59-66	99-107	WTSBQV (SEQ ID NO: 2105)
1889	134-241	157-167	181-189	220-229	1-114	26-35	59-66	99-107	DMWQV (SEQ ID NO: 2109)
1890	138-248	160-172	181-184	220-227	1-122	26-35	59-66	99-107	DMWQV (SEQ ID NO: 2109)
1891	138-248	160-172	181-184	220-227	1-122	26-35	59-66	99-107	DMWQV (SEQ ID NO: 2109)
1892	134-267	158-171	187-193	224-236	1-119	26-35	59-66	99-111	YVLSAAYVQV (SEQ ID NO: 2107)
1893	144-254	165-178	194-200	233-243	1-126	26-35	59-66	99-111	YVLSAAYVQV (SEQ ID NO: 2107)
1894	139-249	161-179	189-195	228-238	1-122	26-35	59-66	99-111	YVLSAAYVQV (SEQ ID NO: 2107)
1895	145-253	164-177	193-199	232-242	1-123	26-35	59-66	99-114	EGQDAATVQV (SEQ ID NO: 2104)
1896	138-245	162-175	184-194	227-234	1-120	26-35	59-66	99-109	EGQDAATVQV (SEQ ID NO: 2104)
1897	138-245	162-175	184-194	227-234	1-120	26-35	59-66	99-109	EGQDAATVQV (SEQ ID NO: 2104)
1898	131-240	153-165	181-187	220-229	1-115	26-35	59-66	99-110	EGQDAATVQV (SEQ ID NO: 2104)
1899	137-247	159-171	187-193	224-234	1-121	26-35	59-66	99-110	EGQDAATVQV (SEQ ID NO: 2104)
1900	138-245	161-171	187-193	224-234	1-122	26-35	59-66	99-111	EGQDAATVQV (SEQ ID NO: 2104)
1901	134-241	157-167	183-189	222-230	1-118	26-35	59-66	99-107	WTSBQV (SEQ ID NO: 2105)
1902	138-245	161-171	187-193	224-234	1-122	26-35	59-66	99-111	EGQDAATVQV (SEQ ID NO: 2104)
1903	137-247	159-171	187-193	224-234	1-121	26-35	59-66	99-111	EGQDAATVQV (SEQ ID NO: 2104)
1904	139-249	162-175	193-199	232-242	1-123	26-35	59-66	99-111	EGQDAATVQV (SEQ ID NO: 2104)
1905	139-249	162-175	193-199	232-242	1-123	26-35	59-66	99-111	EGQDAATVQV (SEQ ID NO: 2104)
1906	139-247	153-163	179-183	218-226	1-114	26-35	59-66	99-103	DMWQV (SEQ ID NO: 2109)
1907	131-233	153-162	178-184	217-227	1-115	26-34	49-65	99-104	DMWQV (SEQ ID NO: 2109)
1908	134-244	158-169	181-191	224-233	1-118	26-35	59-66	99-107	WTSBQV (SEQ ID NO: 2105)
1909	134-244	158-169	181-191	224-233	1-118	26-35	59-66	99-107	WTSBQV (SEQ ID NO: 2105)
1910	134-244	158-169	181-191	224-233	1-118	26-35	59-66	99-107	WTSBQV (SEQ ID NO: 2105)
1911	134-241	155-165	181-187	220-229	1-114	26-35	59-66	99-103	DMWQV (SEQ ID NO: 2109)
1912	133-241	154-164	180-186	219-229	1-117	26-35	59-66	99-106	DMWQV (SEQ ID NO: 2109)
1913	136-246	158-170	184-192	223-235	1-120	26-35	59-66	99-109	DMWQV (SEQ ID NO: 2109)
1914	145-255	169-179	195-201	234-244	1-132	26-35	59-66	101-121	LPPLAAYVQV (SEQ ID NO: 3143)
1915	145-255	169-179	195-201	234-244	1-132	26-35	59-66	101-121	LPPLAAYVQV (SEQ ID NO: 3143)
1916	137-247	159-171	187-193	224-234	1-121	26-35	59-66	99-107	WTSBQV (SEQ ID NO: 2105)
1917	136-246	158-168	184-190	223-231	1-119	26-35	59-66	99-107	WTSBQV (SEQ ID NO: 2105)
1918	136-246	158-168	184-190	223-231	1-119	26-35	59-66	99-107	WTSBQV (SEQ ID NO: 2105)
1919	136-246	158-168	184-190	223-231	1-119	26-35	59-66	99-107	WTSBQV (SEQ ID NO: 2105)
1920	136-246	158-168	184-190	223-231	1-119	26-35	59-66	99-107	WTSBQV (SEQ ID NO: 2105)
1921	136-246	158-168	184-190	223-231	1-119	26-35	59-66	99-107	WTSBQV (SEQ ID NO: 2105)
1922	136-246	158-168	184-190	223-231	1-119	26-35	59-66	99-107	WTSBQV (SEQ ID NO: 2105)
1923	136-246	158-168	184-190	223-231	1-119	26-35	59-66	99-107	WTSBQV (SEQ ID NO: 2105)
1924	137-244	160-174	189-195	232-242	1-123	26-35	59-66	99-111	EGQDAATVQV (SEQ ID NO: 2104)
1925	144-254	166-178	195-201	234-243	1-128	26-35	59-66	99-117	EGQDAATVQV (SEQ ID NO: 2104)

W77D002	1525	135-245	157-169	185-191	224-232	1-119	26-35	30-66	ELWEGADAT (REQ ID NO: 3170)
W77D004	1526	135-245	157-169	183-189	224-232	1-117	26-35	30-66	VEPLUWALAT (REQ ID NO: 3171)
W77D006	1527	135-245	159-171	183-189	226-235	1-121	26-35	30-66	BAITWASWALAT (REQ ID NO: 3172)
W77D007	1528	136-246	159-171	183-189	226-235	1-120	26-35	30-66	NATWASWALAT (REQ ID NO: 3160)
W77D008	1529	136-246	152-165	183-187	220-229	1-118	26-35	30-66	LEIAT (REQ ID NO: 3161)
W77D009	1530	136-246	152-165	183-187	220-229	1-118	26-35	30-66	LEIAT (REQ ID NO: 3161)
W77D010	1531	136-246	152-165	183-187	220-229	1-118	26-35	30-66	LEIAT (REQ ID NO: 3161)
W77D011	1532	136-246	152-165	183-187	220-229	1-118	26-35	30-66	LEIAT (REQ ID NO: 3161)
W77D012	1533	136-246	152-165	183-187	220-229	1-118	26-35	30-66	LEIAT (REQ ID NO: 3161)
W77D013	1534	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D014	1535	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D015	1536	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D016	1537	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D017	1538	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D018	1539	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D019	1540	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D020	1541	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D021	1542	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D022	1543	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D023	1544	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D024	1545	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D025	1546	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D026	1547	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D027	1548	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D028	1549	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D029	1550	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D030	1551	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D031	1552	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D032	1553	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D033	1554	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D034	1555	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D035	1556	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D036	1557	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D037	1558	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D038	1559	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D039	1560	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D040	1561	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D041	1562	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D042	1563	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D043	1564	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D044	1565	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D045	1566	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D046	1567	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D047	1568	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D048	1569	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D049	1570	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D050	1571	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D051	1572	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D052	1573	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D053	1574	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D054	1575	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D055	1576	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D056	1577	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D057	1578	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D058	1579	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D059	1580	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D060	1581	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D061	1582	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D062	1583	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D063	1584	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D064	1585	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D065	1586	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D066	1587	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D067	1588	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D068	1589	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D069	1590	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D070	1591	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D071	1592	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D072	1593	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D073	1594	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D074	1595	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D075	1596	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D076	1597	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D077	1598	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D078	1599	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D079	1600	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D080	1601	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D081	1602	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D082	1603	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D083	1604	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D084	1605	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D085	1606	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D086	1607	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D087	1608	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D088	1609	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D089	1610	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D090	1611	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D091	1612	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D092	1613	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D093	1614	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D094	1615	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D095	1616	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D096	1617	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D097	1618	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D098	1619	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D099	1620	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D100	1621	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D101	1622	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D102	1623	136-246	152-165	183-189	223-231	1-120	26-35	30-66	ELKASWABADY (REQ ID NO: 3173)
W77D103	1624	136-24							

U.S. Patent

Nov. 21, 2006

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7,138,501 B2

1080C08	1315-2409	160-173	189-195	228-238	1-121	26-35	50-66	99-110	GRKYSYGVWFH (SEQ ID NO: 3130)
1080C10	132-243	154-167	182-189	222-228	1-115	26-35	50-66	99-104	DTFLP (SEQ ID NO: 3094)
1080C11	138-249	161-173	189-195	228-238	1-115	26-35	50-66	99-110	EGPTNDAADY (SEQ ID NO: 3143)
1080C12	138-249	161-173	189-195	228-238	1-115	26-35	50-66	99-110	EGPTNDAADY (SEQ ID NO: 3143)
1080D01	172-248	161-173	189-195	228-238	1-120	26-35	50-66	99-109	DETKYDWDY (SEQ ID NO: 3220)
1080D02	172-248	164-177	193-199	235-243	1-125	26-35	50-66	99-114	ETSHSGSGSYFFPDY (SEQ ID NO: 3312)
1080D04	140-244	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SOREQATYYGMADY (SEQ ID NO: 3091)
1080D05	138-244	160-170	186-192	225-235	1-120	26-35	50-66	99-109	EFFQYVLIDY (SEQ ID NO: 3165)
1080D06	138-244	160-172	188-194	227-237	1-121	26-35	50-66	101-110	LYCTGOSGDF (SEQ ID NO: 3186)
1080D09	139-249	161-174	190-196	229-239	1-122	26-35	50-66	99-111	VGNRYTFFH (SEQ ID NO: 3196)
1080D11	136-247	158-171	187-193	226-246	1-119	26-35	50-66	99-104	PLSNVADWDY (SEQ ID NO: 3160)
1080D12	136-247	158-171	187-193	226-246	1-119	26-35	50-66	99-104	PLSNVADWDY (SEQ ID NO: 3160)
1080E01	138-246	160-170	186-192	225-235	1-120	26-35	50-66	99-109	HPVYGLDLY (SEQ ID NO: 3146)
1080E04	137-247	159-172	187-193	226-236	1-120	26-37	52-67	101-109	EGTSGDSDF (SEQ ID NO: 3221)
1080E06	138-248	160-172	188-194	227-237	1-121	26-35	50-68	101-110	EGTSGDSDF (SEQ ID NO: 3221)
1080E07	134-254	165-178	194-200	233-243	1-126	26-35	50-65	99-115	EGTSGAALLTNGAEH (SEQ ID NO: 3130)
1080E09	138-249	160-173	189-195	228-238	1-121	26-35	50-65	99-110	GRKYSYGVWFH (SEQ ID NO: 3130)
1080E12	132-242	154-166	182-188	221-231	1-114	26-35	50-66	99-103	DEFTYANPYLH (SEQ ID NO: 3145)
1080E14	139-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111	ESQTLGERSHLPDY (SEQ ID NO: 3200)
1080E15	143-253	165-176	193-199	235-245	1-126	26-35	50-66	99-115	ESQTLGERSHLPDY (SEQ ID NO: 3200)
1080E16	143-253	165-176	193-199	235-245	1-126	26-35	50-66	99-115	ESQTLGERSHLPDY (SEQ ID NO: 3200)
1080E18	142-251	162-172	188-194	227-237	1-121	26-35	50-66	99-103	NADY (SEQ ID NO: 3121)
1080E19	132-240	154-164	180-186	219-229	1-114	26-35	50-66	99-103	GRYSSSSSYGMADY (SEQ ID NO: 3095)
1080C03	142-250	164-174	190-196	229-239	1-124	26-36	51-66	99-113	VESSES (SEQ ID NO: 3216)
1080C04	133-244	156-171	187-193	226-233	1-115	26-35	50-66	99-104	REGDYVLLHLYGMADY (SEQ ID NO: 3146)
1080G10	145-252	167-177	193-199	232-241	1-127	26-35	50-66	99-116	HDVYGLDLY (SEQ ID NO: 3203)
1080G11	137-247	159-171	187-193	227-237	1-121	26-35	52-67	100-109	LEPDADYDYGDFY (SEQ ID NO: 3214)
1080H01	142-252	164-176	192-198	231-241	1-124	26-37	52-67	100-113	BERGTATQWDFH (SEQ ID NO: 3204)
1080H02	142-252	164-176	192-198	231-241	1-124	26-37	52-67	100-113	BERGTATQWDFH (SEQ ID NO: 3204)
1080H03	146-246	168-178	194-200	233-243	1-125	26-35	50-66	99-112	GRKYSYGVWFH (SEQ ID NO: 3130)
1080H04	135-249	158-170	185-192	223-235	1-118	26-35	50-66	99-110	GRKYSYGVWFH (SEQ ID NO: 3130)
1080H09	137-247	160-173	189-195	228-238	1-121	26-35	52-67	100-109	HDVYGLDLY (SEQ ID NO: 3206)
1080H25	137-247	159-171	187-193	226-236	1-120	26-37	52-67	100-109	HDVYGLDLY (SEQ ID NO: 3206)
1080H36	138-248	160-173	189-195	228-238	1-121	26-35	50-66	99-110	GRKYSYGVWFH (SEQ ID NO: 3130)
1080H37	138-248	160-172	188-194	227-237	1-121	26-35	50-68	101-110	LACTGOSDF (SEQ ID NO: 3186)
1080H38	140-245	162-175	191-197	230-240	1-122	26-35	50-66	99-111	ESQDQDQYALH (SEQ ID NO: 3148)
1080H39	141-249	163-175	189-195	228-238	1-123	26-36	51-66	99-112	RTFSGDSGDFPY (SEQ ID NO: 3215)
1081A01	130-247	153-165	179-185	218-228	1-114	26-35	50-66	99-103	DTIDY (SEQ ID NO: 3203)
1081A02	130-247	153-165	179-185	218-228	1-114	26-35	50-66	99-103	DTIDY (SEQ ID NO: 3203)
1081A03	130-247	153-165	179-185	218-228	1-114	26-35	50-66	99-103	DTIDY (SEQ ID NO: 3203)
1081A06	130-247	151-161	177-183	216-226	1-114	26-35	50-66	99-103	DTIDY (SEQ ID NO: 3203)
1081A08	130-247	152-164	180-186	219-229	1-114	26-35	50-65	99-103	GAASRYEFL (SEQ ID NO: 3118)
1081A09	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107	GAASRYEFL (SEQ ID NO: 3118)
1081A10	133-243	155-168	184-190	223-232	1-117	26-35	50-66	99-106	GDRAEFL (SEQ ID NO: 3119)





2084	137-248	159-172	188-134	227-227	1-120	26-35	50-66	99-109	ELVAGTGGV (SEQ ID NO: 3143)
2085	139-250	161-174	190-136	227-229	1-122	26-35	50-66	99-110	VYVYTGKGAADL (SEQ ID NO: 3172)
2086	139-249	161-173	189-183	228-233	1-121	26-35	50-66	99-111	SVAGRGVETV (SEQ ID NO: 3206)
2087	139-250	161-174	190-136	228-239	1-122	26-35	50-66	99-111	RGCGGGYADLAF (SEQ ID NO: 3146)
2088	141-253	164-177	192-137	227-242	1-123	26-35	50-66	99-114	EGGGGGYADLFT (SEQ ID NO: 2264)
2089	138-242	154-166	182-183	227-231	1-114	26-35	50-66	99-103	ETPTV (SEQ ID NO: 3144)
2090	141-252	163-176	192-138	231-231	1-124	26-35	50-66	99-113	ALGGLGGTGVYDV (SEQ ID NO: 3159)
2091	142-253	164-177	193-159	232-242	1-125	26-35	50-66	99-114	EGGGGYNVATVY (SEQ ID NO: 3160)
2102	135-243	161-177	183-189	222-232	1-117	26-35	50-66	99-106	TDYGGVY (SEQ ID NO: 3692)
2103	139-247	161-171	187-195	224-226	1-121	26-35	50-66	99-110	GVGGGGVPTV (SEQ ID NO: 3162)
2104	139-237	153-163	178-185	218-226	1-114	26-35	50-66	99-103	DTDTY (SEQ ID NO: 2263)
2105	139-240	152-164	180-186	219-229	1-119	26-35	50-66	99-108	SLTGGAADL (SEQ ID NO: 3116)
2106	135-242	154-166	182-184	221-231	1-114	26-35	50-66	99-109	SLTGSPATV (SEQ ID NO: 3120)
2107	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109	SLTGSPATV (SEQ ID NO: 3120)
2108	139-240	153-164	183-186	219-229	1-114	26-35	50-66	99-108	SLTGSPATV (SEQ ID NO: 2263)
2109	135-243	153-163	184-190	223-232	1-117	26-35	50-66	99-106	EVYGGATV (SEQ ID NO: 3157)
2110	139-237	153-163	178-185	218-224	1-114	26-35	50-66	99-103	DTDTY (SEQ ID NO: 2263)
2111	139-237	151-161	178-183	218-226	1-114	26-35	50-66	99-103	DTDTY (SEQ ID NO: 2263)
2112	139-237	151-161	178-183	218-226	1-114	26-35	50-66	99-103	DTDTY (SEQ ID NO: 2263)
2113	139-240	152-164	180-186	219-229	1-114	26-35	50-66	99-108	SLTGGAADL (SEQ ID NO: 3116)
2114	139-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTDTY (SEQ ID NO: 2263)
2115	139-247	157-170	186-192	225-244	1-119	26-35	50-66	99-109	SLTGGAADL (SEQ ID NO: 3116)
2116	135-245	152-164	180-186	218-226	1-114	26-35	50-66	99-103	DTDTY (SEQ ID NO: 2263)
2117	136-240	152-164	180-186	218-226	1-114	26-35	50-66	99-103	DTDTY (SEQ ID NO: 2263)
2118	120-227	140-153	176-202	231-243	1-129	26-35	50-66	99-118	GARYTGGSPATV (SEQ ID NO: 3149)
2119	146-256	164-180	188-195	232-238	1-132	26-35	50-66	99-111	VGKAAVNNVETV (SEQ ID NO: 2197)
2120	139-249	161-178	188-194	227-237	1-122	26-35	50-66	99-111	VGKAAVNNVETV (SEQ ID NO: 2197)
2121	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	VGKAAVNNVETV (SEQ ID NO: 2197)
2122	139-249	161-178	188-195	228-238	1-123	26-35	50-66	99-117	VGKAAVNNVETV (SEQ ID NO: 2195)
2123	145-255	167-179	195-201	234-244	1-128	26-35	50-66	99-117	VGKAAVNNVETV (SEQ ID NO: 2195)
2124	137-247	159-172	188-194	227-235	1-120	26-35	50-66	99-113	VQKQALPFEETV (SEQ ID NO: 3144)
2125	141-251	163-175	191-197	230-240	1-124	26-35	50-66	99-109	ENGCGTGGV (SEQ ID NO: 2195)
2126	137-247	159-172	188-194	227-236	1-120	26-35	50-66	99-109	ENGCGTGGV (SEQ ID NO: 2195)
2127	137-247	159-172	188-194	227-236	1-120	26-35	50-66	99-113	VQKQALPFEETV (SEQ ID NO: 3144)
2128	141-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	VQKQALPFEETV (SEQ ID NO: 3144)



# **Attachment F**



Customer No 000000

ISTMT

DATE PRINTED  
11/10/2010HUMAN GENOME SCIENCES INC.  
INTELLECTUAL PROPERTY DEPT.  
14200 SHADY GROVE ROAD  
ROCKVILLE MD 20850

## MAINTENANCE FEE STATEMENT

According to the records of the U.S. Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O. Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
7,138,501	\$980.00	\$0.00	05/21/10	09/880,748	11/21/06	06/15/01	04	NO	2H PF523 (P1)

# **Attachment G**



DEPARTMENT OF HEALTH & HUMAN SERVICES

RA# 575  
(Master)

OCT 30 2001

Food and Drug Administration  
1401 Rockville Pike  
Rockville MD 20852-1448

Our Reference: BB-IND 9970

Human Genome Sciences, Incorporated  
Attention: Sally D. Bolmer, Ph.D.  
Vice President, Regulatory Affairs  
9410 Key West Avenue  
Rockville, MD 20850

Dear Dr. Bolmer:


We have reviewed the October 4, and 17, 2001, submissions to your **Investigational New Drug Application (IND)** for "Human Monoclonal Antibody IgG1 (HG5) to B Lymphocyte Stimulator (BLyS)."

As discussed during the October 23, 2001, telephone conversation between you and Dr. Jeffrey Siegel of this office, you have satisfactorily addressed the issues raised in our letter of October 11, 2001. The clinical hold has been removed and your proposed study may proceed.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act, and the Code of Federal Regulations (CFR). Progress reports are required at intervals not exceeding one year and are due within 60 days of the anniversary of the date that the IND went into effect [21 CFR 312.33]. Any unexpected, fatal or immediately life-threatening reaction associated with use of this product must be reported to this Division by telephone or facsimile transmission no later than seven calendar days after initial receipt of the information. All serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk, must be reported, in writing, to this Division and to all investigators within fifteen calendar days after initial receipt of this information [21 CFR 312.32].

If you have any questions, please contact the Regulatory Project Manager, Dr. Craig Doty, at (301) 827-5101.

Sincerely yours,



Glen D. Jones, Ph.D.

Director

Division of Application Review and Policy

Office of Therapeutics

Research and Review

Center for Biologics

Evaluation and Research

DEPARTMENT OF  
HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration (HFM-99)

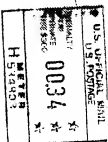
Center for Biologics Evaluation and Research

1401 Rockville Pike

Rockville MD 20852-1448

Official Business

Penalty for Private Use \$300



# **Attachment H**

## BENLYSTA Clinical Trial Summary

<b>Trial</b>	<b>Phase</b>	<b>Patient Population</b>	<b>Study Initiated<sup>1</sup></b>	<b>Study Completed<sup>2</sup></b>
<b><u>IV Controlled Trials in SLE</u></b>				
<b>LBSL01</b>	1	SLE	February 2002	March 2003
<b>LBSL02</b>	2	Active SLE	October 2003	June 2006
<b>BLISS 52</b>	3	Active SLE	May 2007	May 2009
<b>BLISS 76</b>	3	Active SLE	February 2007	March 2010
<b><u>IV Long-term Continuation Trials in SLE</u></b>				
<b>LBSL99</b>	2	Active SLE	May 2005	Ongoing
<b>HGS1066-C1066</b>	3	Active SLE	August 2008	Ongoing
<b>HGS1006-1074</b>	3	Active SLE	June 2008	Ongoing
<b><u>SC Trials in SLE</u></b>				
<b>HGS1066-1058</b>	1	Healthy Volunteers	September 2007	January 2008
<b>HGS1006-1070</b>	2	Active SLE	October 2008	Ongoing
<b><u>RA Trials</u></b>				
<b>LBRA01</b>	2	RA	December 2003	December 2005
<b>LBRA99</b>	2	RA	January 2005	November 2009
<b>HGS1006-C1089</b>	2	RA	September 2009	Ongoing

<sup>1</sup> Date that the first subject was randomized

<sup>2</sup> Date of the last subject's final visit